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UNUSUAL MALFORMATION OF THE LEFT ATRIUM: PULMONARY SINUS

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A RARE anomaly of the left atrium of the heart is presented. This anomaly—in the literature referred to as triatrial heart—was found incidentally at the necropsy of a 70 year old Negro woman, who died four days after being admitted to Cook County Hospital with the clinical diagnosis of hypertensive heart disease and grade 4 decompensation. A detailed report of the necropsy is omitted, since it merely confirmed the clinical diagnosis. The cardiac malformation had no bearing on the clinical picture or the cause of death.

The heart was enlarged, weighing 600 Gm. (body weight, 94 Kg.). The apex was formed by both ventricles. The left ventricular wall was 19 mm., the right 7 mm., thick. The mitral ostium admitted two fingers freely, measuring 10.5 cm. in circumference. The line of closure was slightly thickened, and the mitral ring was partly calcified. The chordae tendineae were not shortened. The aortic ostium measured 7.5 cm., the pulmonary ostium 8.5 cm., in circumference.

The left atrium was almost completely subdivided into an anterior and a posterior part. These two compartments communicated by an almost circular opening close to the left margin of the heart above the attachment of the posterior cusp of the mitral valve. The partition was achieved by a fold originating just to the left of the atrial septum on the posterior wall of the atrium and from its roof. The fold protruded convexly into the anterior part of the atrium; it consisted of a firm plate of connective tissue covered by thin endocardium. The fold ended with a sharp sickle-shaped border facing downward and to the left, bounding the communication between the posterior and the anterior half of the left atrium. The anterior part consisted of a wide central space, into which the posterior part opened. Posteriorly, the anterior chamber extended as a narrow slit between the described partition and the septum atriorum to the posterior wall of the heart. The atrial septum was normal, with a valve of the oval foramen visible on its left surface. The anterior compartment continued into a normally

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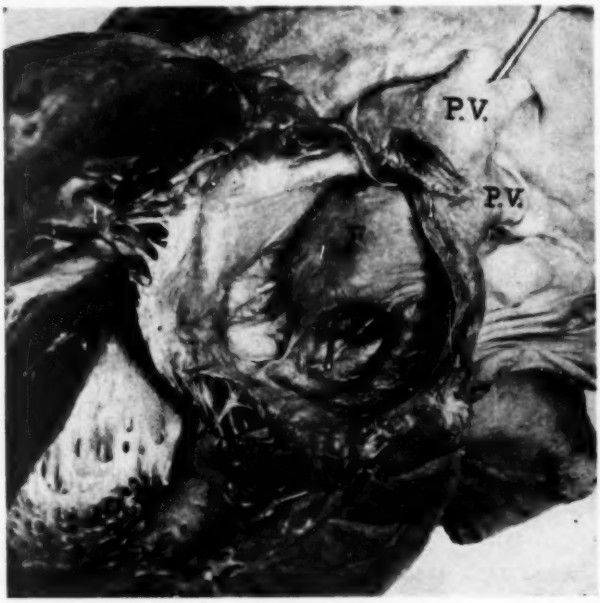
shaped auricular appendage and communicated with the left ventricle through a normal atrioventricular opening.

The posterior compartment of the left atrium received the four pulmonary veins, which were in normal position. The posterior wall of the posterior compartment consisted of cardiac muscle.

Histologically, the fold consisted of dense connective tissue containing a few cardiac muscle fibers; between the collagenous bundles there were elastic fibers which formed a somewhat denser layer in the subendocardial layers.



Left atrium with fold. A probe has been introduced into the upper left pulmonary vein and through the posterior compartment of the left atrium. *P. V.* indicates left pulmonary veins; *F*, the dividing fold.

COMMENT

Previously reported similar cases, listed and reviewed in the papers of Patten and Taggart,[1] Palmer[2] and Pfennig,[3] can be classified into three mains groups:

1. In this group the left atrium is subdivided into two compartments by a diaphragm without any communication between the upper space,

1. Patten, B. M., and Taggart, W. B.: Arch. Path. **8**:894, 1929.
2. Palmer, G. A.: Am. Heart J. **6**:230, 1930.
3. Pfennig, E.: Virchows Arch. f. path. Anat. **307**:579, 1941.

receiving the pulmonary veins, and the lower, which carries the auricular appendage and opens into the left ventricle. In Hagenauer's [3a] patient, a 4 month old baby, the posterosuperior compartment communicated with the right atrium through a patent oval foramen. In Stoeber's [4] patient, dying shortly after birth, part of the pulmonary veins entered the right atrium.

2. The second group comprises cases in which one or several small openings were found in the diaphragm (Potter and Ranson,[5] Palmer,[2] Hosch,[6] William and Abrikosoff,[7] Faber,[8] Borst [8a] and Pfennig [3]). All those who had this type were infants or children, with the exception of Borst's [8a] patient, a 38 year old kyphoscoliotic woman, who died with the symptoms of mitral stenosis; the opening in the dividing septum measured 1 cm.

3. The third group are cases presenting only partial subdivision of the left atrium; there were no clinical symptoms and no other cardiac changes referable to the malformation; they were discovered incidentally at necropsies (Church,[9] Griffith,[10] Fowler [11]). The present case is of this type. In these hearts a fibromuscular band stretches through the left atrium. Behind and above this band the pulmonary veins open, and in front and below, the atrioventricular ostium is found. The bands are of variable width and may even be reduced to cords, described as false tendinous cords, as mentioned by Siegmund in a note to Pfennig's [3] paper.

The different explanations offered by the authors may be grouped as follows:

1. The septum is said to be an overgrowth of the valve of the oval foramen (Fowler,[11] Potter and Ranson,[5] Hosch,[6] Preisz [12] and Griffith [10]). This theory can be easily rejected, since the unaltered foramen ovale can be seen in its proper place.

2. Borst's [8a] theory is that of a primary displacement of the main pulmonary vein; the diaphragm is interpreted as the septum primum

3a. Hagenauer: Frankfurt. Ztschr. f. Path. **41**:332, 1931.

4. Stoeber: Virchows Arch. f. path. Anat. **193**:252, 1908.

5. Potter and Ranson: J. Anat. & Physiol. **39**:69, 1904.

6. Hosch, P. H.: Frankfurt. Ztschr. f. Path. **1**:565, 1907.

7. William and Abrikosoff: Virchows Arch. f. path. Anat. **203**:404, 1911.

8. Faber: Zentralbl. f. Path. **61**:224, 1934.

8a. Borst: Zentralbl. f. Path. **16**:812, 1905.

9. Church, W. S.: Tr. Path. Soc., London **19**:188, 1867.

10. Griffith, T. W.: J. Anat. & Physiol. **37**:255, 1902.

11. Fowler, J. K.: Tr. Path. Soc., London **33**:77, 1881.

12. Preisz: Beitr. z. path. Anat. u. z. allg. Path. **7**:272, 1889.

of Born, which, owing to an increased intensity of growth, formed the whole final atrial septum. The opening in the diaphragm is the ostium primum (Borst,[3a] Stoeber,[4] Patten and Taggart[1] and Faber[6]). All these assumptions are mere speculation and are contradicted by the presence of a regularly formed, though perforated, atrial septum with the limbus and the valve of the oval foramen in proper position. William and Abrikosoff[7] accepted this theory of an anomalous primordium of the primary pulmonary vein but rejected that of the diaphragm as septum primum and the opening as ostium primum on the basis of their microscopic examination. The diaphragm is explained as the result of a splitting of the atrial septums due to the impact of the blood from the misplaced pulmonary vein.

3. The third theory, the principle of which I accept, is the following: The common pulmonary vein has not been incorporated in the left atrium as normally it would have been. The posterosuperior cavity, into which the pulmonary veins open, is the abnormally widened common pulmonary vein, best termed a pulmonary sinus. The septum or diaphragm, complete or incomplete, represents the posterior wall of the primitive left atrium. The first author to assume a failure of fusion of the primitive pulmonary vein and the left atrium was Griffith,[10] one of the earliest describers of this malformation. However, he abandoned this theory for no other reason than that it did not meet with the approval of the members of the society in which he presented his case. Other followers are Palmer,[2] Hagenauer[3a] and Pfennig.[3]

The mechanism by which the anomaly develops has been discussed by Hagenauer[3a] and by Pfennig.[3] The former assumed that the first manifestation of the anomaly went back to that stage of development of the heart in which, according to Spitzer, the two atriums are arranged in a distoproximal sequence. If the primitive pulmonary vein opens at an oblique angle into the distal atrium, an early closure of the opening may occur during the widening of the prospective left atrium. The overexpanded pulmonary vein would later gain a new opening into the right atrium. This explanation is obviously wrong, because the arrangement of the different segments of the heart, according to Spitzer's concept, represents a phylogenetic and not an ontogenetic stage. During the development of a mammalian and a human heart the two atriums are from the beginning arranged side by side. Pfennig,[3] in his explanation of the mechanism of the development of the malformation, assumed that there was a primary occlusion of the primitive pulmonary vein and that this prevented its being incorporated into the left atrium. However, he stated that he did not know why this primary occlusion occurred.

From present knowledge of the development of the heart and the pulmonary vein and from a careful analysis of the cases reported in the literature, the following developmental mechanism is suggested:

The pulmonary vein is at first a single blood vessel, opening into the left atrium close to the line at which the atrial septum is attached to the posterior wall. The single pulmonary vein originates from the confluence of a right and a left pulmonary vein, each composed of two main branches. Very soon the short common terminal part of the pulmonary vein is drawn out and incorporated into the posterior wall of the left atrium, so that in this stage right and left pulmonary veins have gained independent openings into the heart. While the part of the wall of the left atrium between the right and left pulmonary veins grows at considerable speed, the process by which the veins are incorporated into the atrium continues until the common terminal parts of the two left and the two right pulmonary veins also have become part of the left atrium. In this stage the final relations of the left atrium have been established. Its posterior wall is almost in its entirety derived from the wall of the pulmonary vein.

The primary malformation seems to be a failure of the single pulmonary vein to be incorporated into the left atrium, caused in all probability by a disturbance of the normal growth of the posterior wall of the left atrium. The next consequence is a growing disparity between the widening primitive pulmonary vein and its narrow opening into the left atrium. From now on several possibilities of compensatory changes must be considered. The pulmonary vein, bulging against the right atrium, may gain an opening into the right atrium and either the normal left atrial communication may remain as a small defect or the "septum" may close entirely. In the latter case a complete septum will be found between the pulmonary sinus and the left atrium. The sinus opens into the right atrium, and as a further consequence the oval foramen remains patent. In other patients the original opening of the single pulmonary vein experiences early enough a secondary widening, through which later the pulmonary sinus empties its blood into the left atrium. The septum atriorum develops normally, with the limbus and the valve of the oval foramen in normal shape and relation. Finally the widening of the opening of the pulmonary vein into the left atrium may be followed by a dehiscence of the septum between the pulmonary sinus and the left atrium, so that the pulmonary sinus is incompletely separated from the left atrium by a fibromuscular band.

In none of the reported cases had the condition been suspected during life. If the anomaly is not combined with other malformations, the clinical signs should be those of mitral stenosis. Summaries are

found in the papers of Abbot,[13] Poynter,[14] and Bredt,[15] who reviewed congenital malformations of the heart more from the anatomic point of view. It is not mentioned in Taussig's[16] book, which serves primarily clinical interests.

The first author to describe a malformation such as the one reported here was Church[9]; the first to mention it was Andral,[17] who listed it as supernumerary atrium under the heading of "exces de développement du cœur."

SUMMARY

A pulmonary sinus within the left atrium is described, and the malformation is explained by failure of the primary pulmonary vein to be incorporated into the left atrium, owing to a disturbance of the normal growth of the posterior atrial wall. The designation "heart with pulmonary sinus" is suggested instead of "triatrial heart" for malformations of this type.

13. Abbot, M. E., in Nelson's Loose Leaf Medicine, New York, Thos. Nelson & Sons, 1946, vol. 4, p. 207.

14. Poynter, C. W.: Congenital Anomalies of the Heart, Lincoln, Nebraska, University Studies, 1919.

15. Bredt: Ergebn. d. Path. **30**:106, 1936.

16. Taussig, H. B.: Congenital Malformations of the Heart, New York, The Commonwealth Fund, 1947.

17. Andral, G.: Précis d'anatomie pathologique, Paris, Gabon, 1929, vol. 2, p. 313.

APICAL PNEUMONIC SCARS

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IN THE past all apical scars have been considered the result of the action of either the tubercle bacillus or silica. As to the proper division of the scars between these two agents opinions have differed. Some scars are undoubtedly due to silica and others to the tubercle bacillus, but the great majority of apical scars have a characteristic and constant structure by which they may be distinguished from either of the other types. The purpose of this study is to stress the differences between the various types of apical scars and to discuss the cause of the commonest one.

Davson and Susman [1] divided all apical scars into two types, A and B. Type B scars are those which are clearly tuberculous because of the presence of scarred or caseous tubercles. Equal proof is not available for the authors' contention that the commoner type A scars are due to the accumulation of silicious dust. Most of them do contain considerable amounts of silica but, as Belt, Irwin and King [2] have pointed out, the lymphatic channels are obstructed in fibrous scars, and inhaled dust will tend to accumulate in these areas. Some otherwise representative type A scars have little silica in them, and Davson and Susman [1] circumvented this difficulty by suggesting that an inhaled irritant other than silica may be responsible.

More recently, Medlar [3] has reported the results of a macroscopic study of apical scars encountered in a series of 1,259 autopsies. He found that in 106 persons under 20 years of age no such scars were present. The incidence of tuberculosis in this group was 21.7 per cent. In 403 white men over 50 years of age, scars were present in 68.2 per cent, and the lesions were bilateral in 98 per cent. Medlar concluded from this and other observations that apical scars are not etiologically related to tuberculous infection.

To obtain material for the study of this question pulmonary apexes were examined microscopically in a series of 40 autopsies.

From the Department of Pathology, Toronto University.

1. Davson, J., and Susman, W.: J. Path. & Bact. **45**:597, 1937.
2. Belt, T. H.; Irwin, W. A., and King, E. S.: Canad. M. A. J. **34**:125, 1936.
3. Medlar, E. M.: Am. Rev. Tuberc. **55**:511, 1947.

METHOD

If a scar was visible, it was excised and sectioned. Otherwise, a block was taken from the apex in the hope of finding microscopic scars. Three consecutive sections were then cut. One was stained with hematoxylin and eosin, one with Weigert's elastic tissue stain and Van Geison's stain and the third was incinerated and treated with hydrochloric acid by the method described by Irwin.[4] It is obviously easy to miss small tubercles by this method, and therefore, in 4 cases in which on examination of the three sections the scar was classified as nontuberculous, the whole lesion was reexamined by serial section. Every twentieth section was stained and examined.

RESULTS

In the 40 autopsies 17 scars were discovered. One scar was definitely tuberculous. One scar showed nodular silicosis. The remaining 15 were classified in a group by themselves, but 1 of them was transferred into the tuberculous category after serial sections had been made because of the finding of a small healed tubercle. This left 14 scars so similar that one description will serve for all. The pleura was usually not thickened over the scar. The structure was surprisingly uniform, regardless of size in all instances. The alveolar walls stood out in sections stained with hematoxylin and eosin as wavy, brightly stained, eosinophilic, slightly refractile bands of elastic tissue. The alveolar spaces were moderately collapsed and contained pale-staining fibrous tissue composed of thin, parallel strands (fig. 1). Large, dilated bronchi filled with exudate were often present. Branches of the pulmonary artery were narrowed by endarteritis obliterans. Anthracotic pigment was scattered throughout in varying quantities but never in nodular clumps. The distinguishing characteristics were the uniformity and the clearly outlined alveoli filled with fine strands of fibrous tissue. In the sections stained for elastic tissue (fig. 2), the alveolar walls were clearly outlined. The elastic fibers had contracted and stained deeply.

There was a marked variation in the amount of deposit left after the incineration and hydrochloric acid treatment. The amount of silica paralleled the amount of anthracotic pigment throughout the remaining lung and the pigment in the scar itself. There was no relation between the concentration of the silicotic residue and the amount of fibrous tissue in the scar. The deposit was scattered at random and not in nodules. Sometimes the amount of silica was very small, but in no scar was it lacking.

COMMENT

The possible etiologic factors responsible for these fourteen scars can conveniently be discussed under several headings, and many possible causes of apical scarring can be ruled out.

Classic Tuberculosis.—The absence of follicular lesions, nodular fibrosis or caseation rules out the possibility of fibrocaseous tuberculosis.

Exudative Tuberculosis.—According to Jaffé,[5] pulmonary scars may be produced by nonresolution of an exudative type of tuberculosis in the absence of true tubercle formation or caseation. The fact that in 1 of the 4 cases in which a scar was sectioned serially the lesion

4. Irwin, W. A.: Canad. M. A. J. **31**:135, 1934.
5. Jaffé, R. H.: Arch. Path. **18**:712, 1934.

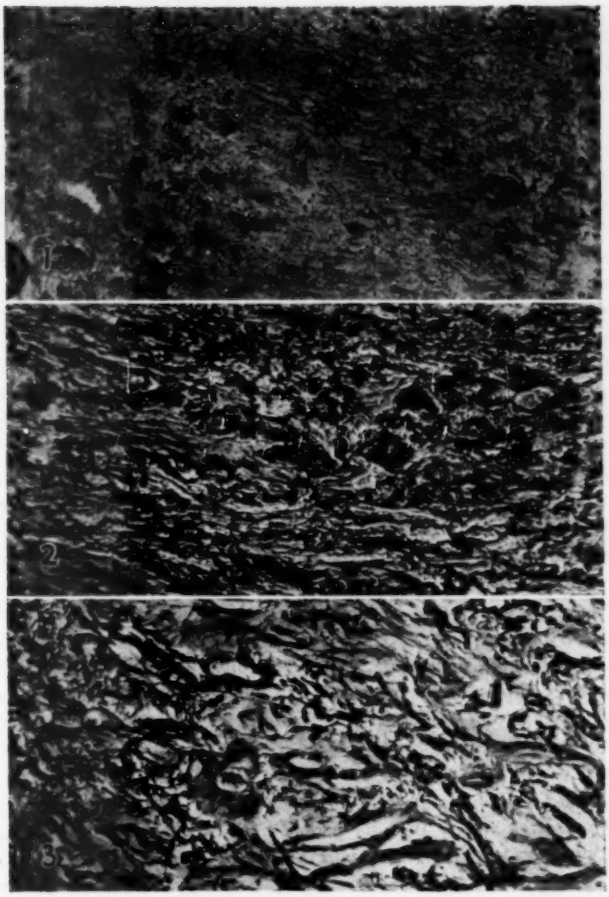

Fig. 1.—Photomicrograph of an apical scar. The alveolar walls are intact, and fine fibrous tissue fills the alveoli. Hematoxylin and eosin; × 67.

Fig. 2.—Photomicrograph of the same scar. The alveolar walls are clearly visible. Weigert's elastic stain; × 67.

Fig. 3.—Photomicrograph of an area of fibrosis outside a silicotic nodule in the apex. Broad bands of collagen cut the elastic tissue into fragments. Weigert's elastic stain; × 180.

had to be transferred to the tuberculous group raised the question whether all these scars had a tuberculous origin. The statistics produced by Medlar [5] on age incidence of apical scarring and tuberculosis make this unlikely. There is a possibility that in the case in question tuberculosis was a complicating factor in the more usual type of scar. Undoubtedly, if all the scars had been sectioned serially, more tubercles would have been found.

Nodular Silicosis.—To quote from a recent paper of Costero's [6]:

> . . . The histological basis of all lesions induced in the human lung by silicious dust is the proliferation of reticular fibers. After proliferation these fibers are partially or wholly transformed into collagen and undergo hyalinization and retraction. . . . The elastic fibers disappear in the completely constituted lesions. Their disposition outside the latter is indicative of traction initiated by shrinkage.

Figure 3 is a photomicrograph of a field outside a silicotic nodule. Broad bands of collagen cut the elastic tissue into fragments. The contrast between it and the common type of apical scar (figs. 2 and 3) is striking.

Silicotic Reticulosis.—In the early reticular lesions of silicosis there is thickening of the periarterial connective tissue by dust and reticulin fibers. Surrounding alveoli are compressed and there is no development of fibrous tissue in the alveolar spaces.

Acute Infarction.—Recent infarcts are not commonly observed in the apex, and acute infarction does not occur in otherwise normal lungs. The high incidence of apical scars would therefore be difficult to explain on the basis of infarction. Furthermore, the elastic pattern is not preserved in a healed infarct.[7]

Chronic Infarction.—It has been mentioned that branches of the pulmonary artery are narrowed in these scars. Dock [8] pointed out that the effective pulmonary artery pressure at the apex in the erect posture is almost nil. It must be considered whether this in itself could produce an obliterative endarteritis of the pulmonary artery and consequent slow ischemic scarring of the apex. The histologic picture would still not correspond.

Collapse.—It is an established fact that respiratory movement is minimal at the apex. In older people who, because of sedentary habits of occupation and relaxation, never inspire deeply, the collapse of a few apical alveoli is easy to visualize. If then fibrous strands were to develop in the alveoli, this collapse would be made permanent and a typical scar would be produced. However, respiratory movement is equally poor along the posterior lung border close to the hilus,

6. Costero, I.: Am. J. Path. **24**:49, 1948.
7. Castleman, B.: Arch. Path. **30**:132, 1940.
8. Dock, W.: Am. Rev. Tuberc. **53**:297, 1946.

and similar scars are not found in this location. Parenchymal scarring is also not a complication of therapeutic collapse.

Pneumonia.—Castleman [7] described these scars as the result of organized tuberculous pneumonia. For the reasons already given, I do not agree that the pneumonia is invariably tuberculous. From consideration of the histologic characteristics, I think that the scars are the result of a low grade inflammation. The incidence of lobar and bronchopneumonia is not high enough to make them likely causes. Primary atypical pneumonia, however, is very common and may involve the apex; it is possibly the prime factor in many of these scars. The peculiar localization of the scarring is probably dependent on two factors: poor apical movement and a very low effective arterial pressure. The important fact is that these scars are the result of an old pneumonia and in most cases not a tuberculous pneumonia.

SUMMARY

Apical scars were collected for microscopic study from a series of autopsies. Three types of scars were found, tuberculous, silicotic and a third type, which was the commonest. The common type of apical scar, in which the alveolar pattern remains intact, is the result of an organized pneumonia which is in most cases not tuberculous.

COARCTATION OF THE AORTA WITH DEATH FROM RUPTURE OF A CEREBRAL ANEURYSM

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THE ASSOCIATION of coarctation of the aorta and cerebral aneurysm is an interesting one. The following case, published with the permission of Prof. S. J. Hartfall, is the sixteenth recorded and the eleventh in which death occurred from rupture of the aneurysm, both coarctation and cerebral aneurysm being demonstrated at autopsy in each case.

REPORT OF A CASE

P. M., a single woman aged 19, while at work in a clothing factory was seized with severe headache and vomiting; she then collapsed, and died about nine hours later. The previous day she had complained of slight headache but had otherwise been perfectly well. Her mother described her as a bright girl who was always on the move, the most active of her seven children. This girl had led an energetic life, had played games while at school, was later in the Women's Land Army and went dancing nearly every evening. When excited, it was particularly noticed, she became red in the face. At the age of 2 she had whooping cough, at which time a doctor had remarked that she had a "strained heart."

On being admitted to the Leeds General Infirmary she was found to be drowsy. with a pale ashen face and cyanosed lips, but could be roused by persistent questioning. There was urinary incontinence.

Examination revealed rigidity of the neck and Kernig's sign. The pupils reacted to light, and the fundi showed multiple hemorrhages. Muscular tone was diminished in the left leg; the left knee jerk was absent, and there was left ankle clonus. Lumbar puncture showed a pressure of spinal fluid of 100 mm. of water, rising freely on compression of the jugular vein; the fluid was blood stained. The pulse was completely irregular, with a rate of 98. The apex beat of the heart was situated 4½ inches (11.5 cm.) from the midline and was irregular, with a low-pitched diastolic murmur; the first and second aortic and pulmonary sounds were split.

Subarachnoid hemorrhage, probably due to ruptured aneurysm, was diagnosed.

The coarctation was overlooked, not surprisingly, since the serious cerebral complication made careful examination difficult.

Autopsy.—The body was that of a spare young woman, weighing 91 pounds (41 Kg.). The heart weighed 10½ ounces (297.5 Gm.), and there was some hypertrophy of the left ventricle. The myocardium was firm and healthly looking. There was a congenital bicuspid aortic valve, one cusp taking the place of the anterior and left posterior cusps. A slight valvular patency of the foramen ovale was present. The coronary arteries showed patches of atheroma without any narrowing. The aorta was normal in size up to a point just beyond the origin of

From the Department of Pathology, University of Leeds.

the left subclavian artery, where it rapidly narrowed to a diaphragm-like stenosis with a small central opening 2.5 mm. in diameter. Proximal to this coarctation, atheromatous streaking was evident in the aorta and was particularly well marked in the common carotid arteries. Immediately below the constriction the aorta widened to a caliber only slightly less than that of the proximal part. The abdominal aorta was hypoplastic, especially below the origin of the renal arteries. There was no atheroma distal to the stenosis.

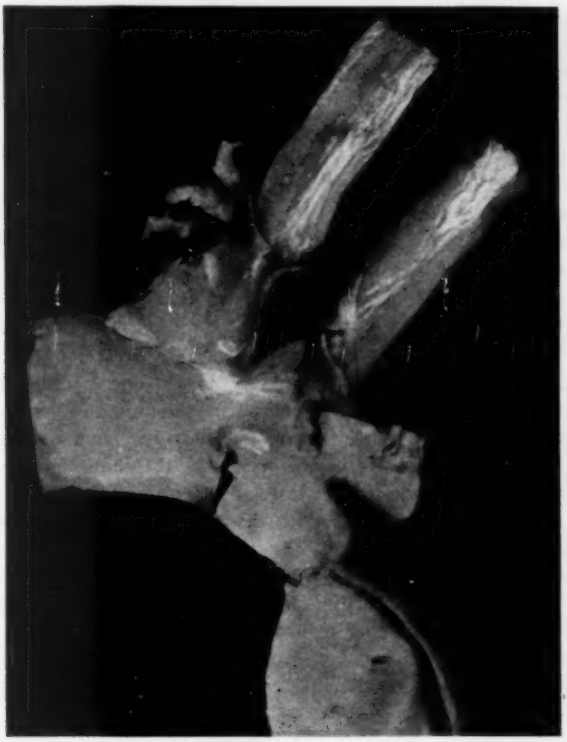

Fig. 1.—Coarctation of the aorta and proximal atheroma, the latter especially evident in the common carotid arteries; × 0.80.

The brain showed some flattening of the cerebral convolutions. There was extensive subdural hemorrhage over both hemispheres, with subarachnoid hemorrhage at the base, particularly around the pons and between the frontal lobes. Situated on the left anterior cerebral artery at its junction with the anterior communicating artery there was a small aneurysmal sac embedded in recent blood clot. The aneurysm in its collapsed state measured about 0.7 cm. in diameter and had ruptured on its deep aspect. The hemorrhage had caused much destruction

of the adjacent frontal lobes and on the left side had entered the lateral ventricle. The basal ganglions on both sides showed petechial hemorrhages. The vessels at the base of the brain showed no sign of atheroma; it is most probable that the aneurysm was of a developmental type.

The other organs showed no notable changes and appeared healthy.

COMMENT

Coarctation of the aorta is not a common lesion. From the time of the earliest reported case in 1791 up to 1928 Abbott [1] collected 200 cases of the "adult type" in which autopsies had been made, and since the latter date Reifenstein, Levine and Gross [2] have reviewed a further 104 cases up to 1947, making in all 304 recorded cases.

In 10 cases of coarctation confirmed at autopsy death was found to be due to rupture of a clearly defined cerebral aneurysm. Five of these cases occurred before 1928 and were briefly reviewed by Abbott. They were recorded by Eppinger (1871, case 2), Kolisko (1913, case 2), Strassman (1922, case 7), Woltman and Shelden (1927, case 1) and Parkes Weber (1927). Since this review 5 further cases have been reported by the following authors: Green [3] (1928, case 3), Bode and Knop [4] (1929, case 2), Förster [5] (1940), Bramwell and Jones [6] (1941) and O'Reilly and Chapman [7] (1943).

Analysis of these cases, including the present one, reveals that in 4 of the 11 there was more than one aneurysm present. As noted by Woltman and Shelden,[8] these patients tended to be young and vigorous, and rupture of the aneurysm was evidently the immediate result of physical strain, as in the present case. Abnormally high blood pressure must have been present in every case, as hypertrophy of the left ventricle was found in each. The average age was 23 years; the youngest patient was 13 and the oldest 40, and 9 of the patients were males. The ruptured aneurysms ranged in size from a hempseed to a walnut, and it is interesting to note that the largest aneurysms were found in the oldest patients; both patients aged 40 had large aneurysms. The other patients were all under 26 and had small aneurysms with

1. Abbott, M. E.: Am. Heart J. **3**:574, 1928.

2. Reifenstein, G. H.; Levine, S. A. ,and Gross, R. E.: Am. Heart J. **33**:146, 1947.

3. Green, F. H. K.: Quart. J. Med. **21**:419, 1928.

4. Bode, O. B., and Knop, F.: Deutsches Arch. f. klin. Med. **163**:298, 1929.

5. Förster, A.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **33**:115, 1940.

6. Bramwell, C., and Jones, A. M.: Brit. Heart J. **3**:205, 1941.

7. O'Reilly, J. N., and Chapman, O. W.: Arch. Dis. Childhood **18**:109, 1943.

8. Woltman, H. W., and Shelden, W. D.: Arch. Neurol. & Psychiat. **17**:303, 1927.

the exception of Green's patient whose aneurysm was 3 cm. in diameter. All the ruptured aneurysms arose from intracranial branches of the internal carotid arteries.

A further case of coarctation and cerebral aneurysm confirmed at autopsy was recorded by Davies and Fisher[9] (1943). Their patient, a youth aged 17, died of a ruptured aorta, and a small aneurysm with evidence of previous leakage was found on the left middle cerebral artery.

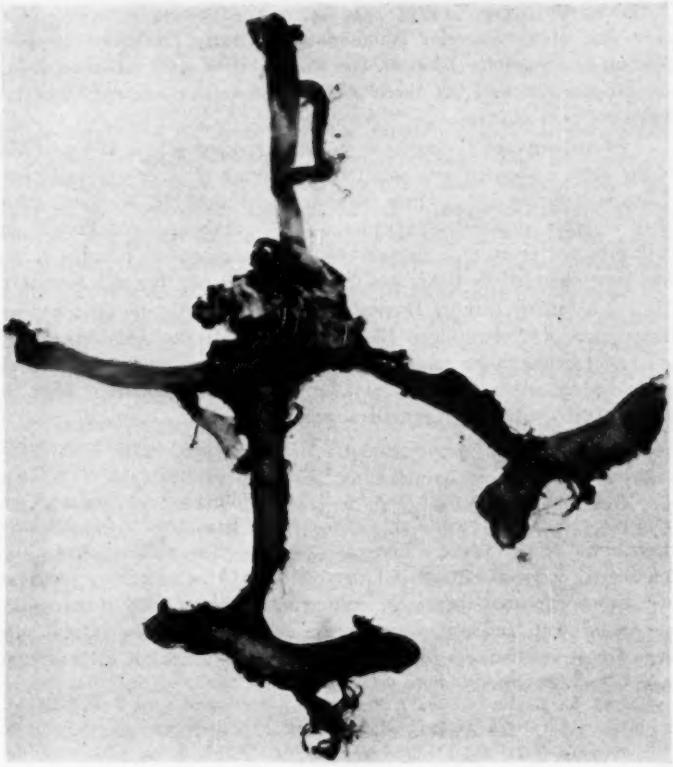

Fig. 2.—Ruptured cerebral aneurysm at the junction of the left anterior cerebral and anterior communicating arteries; × 3.5.

Four cases are recorded in which coarctation and an unruptured cerebral aneurysm were found at autopsy, the patient dying from some other condition. In all 4 the aneurysm involved either the basilar or one

9. Davies, J. N. P., and Fisher, J. A.: Brit. Heart J. **5**:197, 1943.

of the vertebral arteries. Abbott, in her review, mentioned 2 of these cases, those of Knierim (1880, basilar) and Sommerbrodt (1883, vertebral). Boyd and Werblow [10] recorded a further case (vertebral) in 1938, and Walker and Livingstone [11] (case 2) the fourth (vertebral), also in 1938. In the last instance subarachnoid hemorrhage had occurred, but although the left vertebral artery showed irregular saccular aneurysmal dilatations no definite rupture was found; the patient also had infective endocarditis.

Walsh and King [12] (1942, case 4) recorded a case of rupture of an aneurysm of the anterior communicating artery confirmed by postmortem examination. Probable coarctation of the aorta was recorded on clinical examination, but there is no mention of confirmation of this diagnosis post mortem.

Lichtenburg and Gallagher [13] in 1933 reported a case of coarctation of the aorta associated with intermittent leakage of a cerebral aneurysm, diagnosed during life. Their patient, a girl aged 12, was still living after eighteen months' observation. These authors could find in the literature no record of a similar condition diagnosed in life, but a case was later recorded by Baker and Shelden [14] (1936), that of a woman of 25, and a further case by Davies and Fisher (1943), the already mentioned case of a youth aged 17. In the last case the diagnosis of subarachnoid hemorrhage was confirmed by lumbar puncture and that of aneurysm by postmortem examination thirteen months later, after the patient had died of a ruptured aorta.

SUMMARY

An active, healthy girl of 19 collapsed suddenly and died and was found at autopsy to have a ruptured cerebral aneurysm associated with coarctation of the aorta. Ten cases with similar findings have been found recorded in the literature, together with 1 case of leaking aneurysm and 4 of unruptured aneurysm, making a total of 16 cases of coarctation associated with cerebral aneurysm in which the diagnosis was confirmed post mortem. A further 3 cases are recorded but without postmortem confirmation.

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SEVERE ADRENAL CORTICAL ATROPHY (CYTOTOXIC) AND HEPATIC DAMAGE PRODUCED IN DOGS BY FEEDING 2,2-BIS(PARACHLOROPHENYL)-1,1-DICHLOROETHANE (DDD OR TDE)

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FOLLOWING the feeding of the insecticide 2, 2-bis(parachlorophenyl)-1,1-dichloroethane, commonly called DDD or preferably TDE, to dogs for periods of one to thirty-three months there was observed on both gross and microscopic pathologic examination an unusually consistent and severe atrophy of the adrenal cortex of the type generally designated as cytotoxic. Such a lesion has not been seen in the microscopic examination of over 300 other dogs in this laboratory following the usually prolonged feeding of about fifty other chemical compounds. Some of the compounds had produced severe damage of the liver or other organs, but rarely had they affected the adrenal glands in any manner, and none had caused adrenal lesions similar to those reported here. In particular, the closely related compounds DDT (2,2-bis(parachlorophenyl)-1,1,1-trichloroethane), methoxychlor and DDT dehydrochloride when administered to dogs in the same manner as TDE did not affect the adrenal glands. As stated in a preliminary note,[1] this is a striking example of chemical specificity in the causation of damage of an organ.

MATERIALS AND METHODS

Eleven young adult dogs were fed TDE dissolved in corn oil in capsules at levels of 50 to 200 (usually 50 or 80) mg. per kilogram per working day. The dosage levels were kept constant. Seven of the dogs were mongrels and 4 were Irish terriers; 6 were female and 5 were male. Gross and microscopic pathologic examination was done on each of the 7 dogs that died and the 3 that were killed. One dog is still living and in apparent good condition thirty-eight months after the beginning of the experiment.

From each of the 10 dogs studied, hematoxylin-eosin stained paraffin sections of formaldehyde-fixed tissue were made from heart, liver, gallbladder, spleen, lymph nodes, pancreas, kidney, adrenal gland, thyroid gland, parathyroid gland,

From the Division of Pharmacology, Food and Drug Administration, Federal Security Agency.

1. Nelson, A. A., and Woodard, G.: Federation Proc. **7**:277, 1948.

hypophysis, ovary (or testis) and uterus (or prostate); also frozen sections of kidney and liver were stained for fat with oil red O, and a Wright-Giemsa-stained smear of the bone marrow was made. Paraffin sections of lung and stomach and a frozen section of adrenal gland stained for fat were made from 9 dogs, and paraffin sections of thigh muscle, small intestine, colon, urinary bladder, rib bone, bone marrow and four levels of brain were made from 8 dogs. In several instances each, adrenal gland, liver and kidney were also fixed in Zenker's and/or Helly's fluid, and a Mallory type of differential connective tissue stain was made.

EFFECTS OBSERVED

Dosage of TDE, duration of feeding, etc., are given for each dog in the table. "M" in the dog number indicates that the animal was a mongrel; the others were Irish terriers. Changes resulting from treatment observed in the dogs during life were relatively slight. There was generally slight or moderate loss of weight, up to as much as 25 per cent of the initial weight. Much of this loss occurred in the last week or so of life, coincident with weakness and anorexia, which came on

Experimental Conditions for Individual Dogs

Dog	Sex	Age at Death, Mo.	Time on Experiment, Mo.	Dosage of TDE, Mg. per Kg. per Day	Weight at Start, Kg.	Weight at Finish, Kg.	Manner of Death
M-200	M	17	2	200	11.5	8.6	Died
M-198	M	16	2½	100	11.5	9.8	Killed
90-219	F	16	2½	80	9.9	7.7	Killed
M-228	M	(?)	1	80	7.0	6.0	Died
M-225	F	12	4	80	9.5	7.6	Died
M-196	M	33	20	50	9.5	9.0	Died
82-199	F	51	17	80	8.2	8.0	Died
M-201	F	38	21	50	8.3	8.3	Died
82-198	M	56	21	50	10.4	10.4	Killed
M-202	F	51	33	80	7.5	7.3	Died
90-218	F	Alive	38	50	11.0	...	.....

relatively suddenly. There were no convulsions or other neurologic symptoms. No pigmentary changes were noted.

GROSS PATHOLOGIC CHANGES

Slight or moderate emaciation was present in some of the dogs, corresponding to the loss of weight noted in these animals during life.

The adrenal glands of all the dogs, including the dog killed while apparently in good condition, were distinctly reduced in size. On section, this was accounted for by marked thinning of the cortex, which was also a deeper yellow than usual. The medulla appeared unaffected. The adrenal glands of dogs 82-198, M-201 and M-202, after formaldehyde fixation, were carefully trimmed of surrounding connective tissue and weighed; the respective combined weights were 0.50, 0.47 and 0.48 Gm. The adrenal glands of 3 control dogs of similar weight gave values of 0.82 Gm. (2 dogs) and 0.87 Gm. (1 dog) after similar treatment. Baker's [2] figures for the mean adrenal weights of dogs weighing 8.6 Kg. (average weight of the 3 TDE dogs at the time of death) are considerably higher, namely 1.14 Gm. for females in diestrus and 1.12 Gm. for mature males. The variation between different observers in the degree of careful trimming of extra-adrenal tissue, a rather time-consuming chore, is probably a large factor in such differences of weight.

2. Baker, D. D.: Am. J. Anat. **60**:231, 1937.

The liver in most instances had a moderate or marked nutmeg appearance, with a yellowish background contrasting with the dark red lobular centers. The two exceptions were dogs 82-198 and 82-199, affected respectively with slight and moderate hepatic cirrhosis, about which more will be said under "Comment."

The kidneys of several dogs showed on section prominent whitish yellow to light orange fine radial streaking of the cortices, an accentuation of the fainter streaking normally present. Apart from this, the kidneys were normal in appearance.

Organs other than the adrenal gland, liver and kidneys showed no consistent gross changes. A few incidental lesions, each occurring in only 1 dog and of uncertain relation to the treatment, will be considered together with their microscopic appearances under that heading.

MICROSCOPIC PATHOLOGIC CHANGES

Adrenal Gland.—Like the macroscopic appearance, the microscopic appearance of the adrenal gland was uniform throughout this series of dogs. Such slight variations of the microscopic picture as were present appeared to be related to the differing ages of the lesions; there was little variation in intensity.

The adrenal cortex was strikingly reduced in width, being in all instances no greater than about half the usual thickness, while in the extreme examples the thickness was about one-fifth the normal (figs. 1 *B*, *C* and *D*). The normal structure was highly disorganized (figs. 2 *A*, *B* and *C*). The zona glomerulosa was the best retained of any of the cortical zones, but it showed at least slight (in the dog killed while in apparent good health) and often marked changes in the form of loss of outline of the zone and of enlargement, rounding and foaminess of the individual cells. The zona fasciculata was shortened, the individual cords were irregular, and the cells showed the same types of alteration as did those of the zona glomerulosa. The zona reticularis had essentially vanished. Because of the loss of glandular cells from the inner portion of the cortex, there was usually an appearance of fibrosis in the juxtamedullary region, looser in the earlier examples and denser in the later ones. However, collagen stains of the Mallory type showed that most of this apparent fibrosis could be accounted for by condensation of the preexisting stroma.

Cortical inflammatory or necrotizing phenomena were never massive, but enough were present to suggest a slow, continuing process of damage with at least some coincidental attempt at repair. More of these changes were seen with the shorter than with the longer periods of survival. In the outer part of the cortex particularly, individual cells or small groups of cells showed fragmentation or pyknosis of the nuclei and/or oxyphilia or partial loss of the cytoplasm. At the same time small, undifferentiated cells appeared to be enlarging and differentiating into cortical cells. Other histologic features indicating a process other than simple atrophy were the irregularities of size and shape already noted in the individual cells and cell cords, and a mild degree of mobilization of small mononuclear and rare polymorphonuclear cells. No unquestionable mitotic figures were seen, and nothing even resembling adenomatoid hyperplasia was present. In the dogs surviving for the longer periods, the innermost cortical cells became even foamier and more like macrophages in appearance than previously and contained in addition to much lipoid material a small amount of finely divided, light brown pigment.

Vascular abnormalities in and around the adrenal glands were looked for and were absent. In frozen sections the content of sudanophilic material and of doubly refractile material in such cortical cells as remained was not diminished. The adrenal medulla was uniformly uninvolved and gave its usual chromaffin reaction

with fixatives containing potassium bichromate. Accessory cortical tissue is rare in dogs and was not noted in any location in this study.

Liver.—Moderate or severe fatty degeneration was present in the liver of every one of the 10 dogs except the one killed while in apparently good condition. Moderate centrolobular atrophy and more or less centrolobular congestion were generally present; the congestion was apparently secondary to the atrophy of hepatic cells, since elsewhere in the body evidences of chronic congestion were absent. Present in from one third to two thirds of the dogs were slight

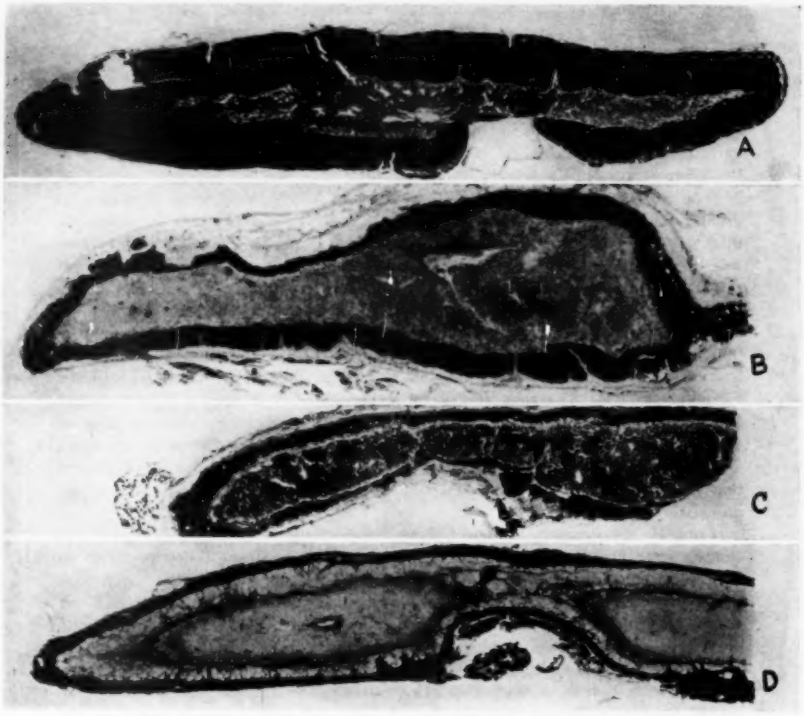

Fig. 1.—*A*, frozen section of an adrenal gland of a control dog of the same weight as the average of those fed TDE; stained with oil red O and counterstained with hematoxylin; low magnification. The magnification of B, C, and D in this figure is greater than that of A.

B, frozen section of an adrenal gland of dog M-225; same stain as in *A*. Note the great reduction in the width of the cortex (darker portion).

C, frozen section of an adrenal gland of dog M-201; same stain as in *A*. Note the great reduction in the width of the cortex (darker portion).

D, frozen section of an adrenal gland of dog 82-198; Mallory connective tissue stain. Note the small amount of fibrous tissue between the markedly narrowed cortex and the medulla as compared with the larger amount in the capsule. It is apparent that any cortical fibrosis present is chiefly relative, from loss of parenchyma.

periportal fibrosis, slight proliferation of small bile ducts, slight portal lymphoid cell infiltration and portal macrophages containing small amounts of hemosiderin. Only in the dog surviving for the shortest period, thirty-four days, was there definite necrosis of hepatic cells.

Kidney.—The kidney was unaffected by TDE except that the average fat content of the tubular epithelium was about double the normal. In our experience this is a fairly common and nonspecific reaction of the dog kidney to toxic agents. Glomeruli and blood vessels were unaltered, and no "spontaneous" nephritis was present.

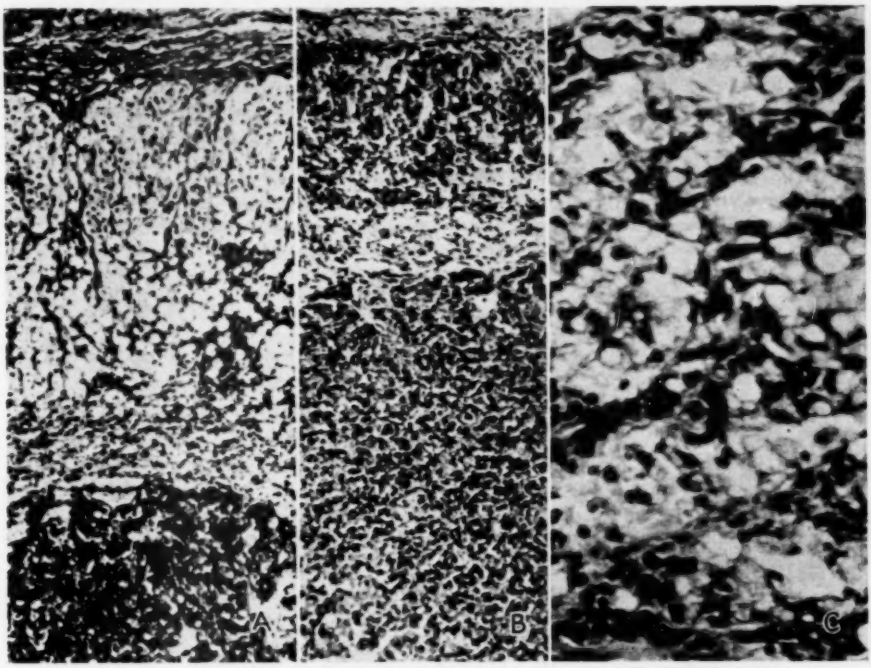

Fig. 2.—*A*, section of an adrenal gland of dog M-198; hematoxylin-eosin stain; medium magnification. Note the foamy appearance of the remaining cortical cells and the marked narrowing of the cortex. The edge of the medulla occupies the lower third of the print.

B, section of an adrenal gland of dog 82-198; same stain and magnification in *A*. Note the even greater narrowing of the cortex, now only a thin rim. About half the thickness of the medulla is shown below.

C, portion of adrenal cortex of dog 90-219, showing the foamy appearance of the remaining cortical cells, and smaller cells of various types as described in the text; high magnification.

Bone Marrow.—The marrow showed slight changes, of the type often seen accompanying death from toxic substances. With some inconsistencies, there were on the average a slight increase in the myeloid-erythroid ratio, a reduction in the number of mature granulocytes and a slight shift to the left in the myeloid line,

the metamyelocytes and myelocytes being increased in number. These changes were judged from inspection of both sections and smears; counts were not made. In at least 2 dogs, it was thought, the erythroid elements were decreased in absolute number.

Incidental Lesions.—As mentioned in connection with the gross description, there were a few lesions, each occurring in but 1 dog, which were of uncertain relation to treatment or at least not in causative relation to the adrenal lesions. To save space, only the diagnoses will be given here. Each of the lesions was visible grossly as well as microscopically. The lesions were moderate subacute focal myocarditis in dog M-200, marked erythrophagia of recent appearance in the mesenteric lymph nodes of dog M-198, a small amount of recent mucosal hemorrhage in the neck of the urinary bladder of dog M-228, a moderate amount of recent hemorrhage of the stomach mucosa in dog M-201, focal papillary proliferation of the prostatic epithelium in dog 82-198 and massive pyometra in dog M-202. The total amount of parasitism in this group of dogs was relatively small.

Other Structures.—The spleen contained a possibly slight excess of hemosiderin over the small amount normally present. Except for the incidental possibilities mentioned in the previous paragraph, lymph nodes, heart, gallbladder, lungs, pancreas, stomach, intestines, urinary bladder, thyroid and parathyroid glands, ovaries, uterus, testes, prostate, voluntary muscles, brain and hypophysis were not affected by TDE, and in all these structures the microscopic appearance was that seen in normal young adult to middle-aged dogs.

COMMENT

From the chemical point of view the adrenal lesion described is a remarkable example of chemical specificity as related to damage of an organ. From the pathologic point of view the considerable morphologic resemblance to human Addison's disease of the idiopathic or cytotoxic type raises the question of the possible position of various chemicals in the etiology of the human condition. However, we simply state the latter possibility and do not wish to stress it. We do not infer that human beings rather heavily exposed to TDE, e. g., pest control operators, are necessarily liable to adrenal damage. In all probability, some people react to a toxicant more in the fashion of a rat than a dog, and other people do the opposite. Since man is now exposed to an ever increasing number of chemicals, it becomes of some importance to determine the similarities and differences of human and animal reactions to these chemicals.

Perhaps first a brief mention of the proper name for the pathologic process seen in these dogs may be appropriate. We have labeled it "severe cortical atrophy" with the alternative designation of "cytotoxic" to agree with the more common name for the similar morphologic picture seen in man. The process is certainly not a simple type of atrophy such as may occur in certain other organs during slow starvation or in the adrenal gland itself following hypophysectomy or treatment with adrenal cortex extracts. Actually, it seems to be a slow necrosis with a certain amount of simultaneous attempt at repair, and the histologic features indicating this have already been stated. Other

names for this type of adrenal lesion of man are given by Weiner.[3] In a recent and detailed discussion Friedman [4] used the term "adrenocortical contraction."

Spontaneous disease of the adrenal cortex of a type histologically comparable to certain forms of Addison's disease seen in man apparently does not occur in animals, judging from a reasonably thorough search of the literature. Such a condition, on the basis of subtotal vascular occlusion, has been produced by the experimental surgical procedures of Rogoff,[5] principally in cats. We have seen no previous reports of its having been produced in animals on the basis of chronic toxicosis except to a limited degree in guinea pigs by Humphreys and Donaldson,[6] who used a German preparation of the type of suramin sodium U. S. P. We do recognize that less severe atrophies of a more simple type have been produced on such a basis and that severe acute damage of the adrenal gland has been produced by a variety of methods. Implication of chemical toxicants in human Addison's disease seems limited to the aforementioned German proprietary drug (germanin or Bayer 205).[7]

We have done no blood chemical, hematologic, hormonal or metabolic studies on the dogs reported on in this paper.

Only 2 of the dogs had been used in previous toxicity experiments. Strangely enough, these were the only 2 that showed cirrhosis of the liver grossly and microscopically; the condition was pronounced in dog 82-199 and of lesser degree in dog 82-198. A year and a half previously these 2 dogs had finished an eight months' course of feeding of 100 mg. of 3-methyl-4-(4-diethylamino-1-methylbutylamine)-7-chloroquinoline (SN 6911, an antimalarial drug) per kilogram per day, apparently without effect. (Two other dogs given the same course of feeding of this drug had shown only minor alterations of the liver on microscopic examination; these dogs, however, were mongrels, while the 2 later given the TDE were purebreds).

Bronchopneumonia or other infection as a contributing cause of death was essentially absent; the one exception was dog M-202, which died of pyometra nine days after being mated.

The animal toxicity studies of TDE (DDD) reported in the literature include those of Lillie and associates [8] and Haag and associates.[9] The former studied 8 rabbits treated for periods up to

3. Weiner, H. A.: Am. J. Path. **12**:411, 1936.
4. Friedman, N. B.: Endocrinology **42**:181, 1948.
5. Rogoff, J. M.: Arch. Path. **38**:392, 1944.
6. Humphreys, E. M., and Donaldson, L.: Am. J. Path. **17**:767, 1941.
7. Wells, H. G.; Humphreys, E. M., and Work, E. G.: J. A. M. A. **109**:490, 1937.
8. Lillie, R. D.; Smith, M. I., and Stohlman, E. F.: Arch. Path. **43**:127, 1947.
9. Haag, H. B., and others: Indust. Med. **17**:477, 1948.

thirty-nine days and stated that "the adrenal glands were regularly normal, with lipid depletion of the glomerular zone in 2 of 7." In 2 rats dying acutely, there was "some fatty degeneration of medulla cells in the adrenal glands." Haag and co-workers included the adrenal glands among the organs studied histologically when they exposed dogs, rabbits and rats to this toxicant by a variety of routes, but reported no lesions in them. The dogs had dust atmosphere and spray atmosphere exposure. Unpublished studies of rats, mice, rabbits and 2 monkeys of the Division of Pharmacology of the Food and Drug Administration have shown no adrenal damage from TDE.

SUMMARY

Ten dogs were studied grossly and microscopically after being fed the insecticide TDE (also called DDD; chemically, 2,2-bis [para-chlorophenyl]-1,1-dichloroethane) at levels of 50 to 200, usually 50 or 80, mg. per kilogram per day for periods of one to thirty-three months. In every one there was a high grade of adrenal cortical atrophy of a cytotoxic type. The adrenal cortex was from one half to one third or less of its usual thickness, and microscopically there was much distortion of the normal structure with alteration of the normal cellular appearances. The adrenal medulla showed no changes.

Of some dozens of compounds fed to over 300 of our dogs, none except TDE has caused adrenal cortical atrophy, even though several have caused severe hepatic damage; few have affected the adrenal gland in any way, even though they differed chemically from TDE as little as the presence of a single additional chlorine atom in the molecule.

In other animal species studied by ourselves and others TDE caused little if any adrenal damage.

Males and females, purebred and mongrel dogs, were affected alike. In addition to the adrenal gland the liver was uniformly affected, the principal lesion being fatty degeneration. The kidneys contained a greater than usual amount of fat. Among other structures the hypophysis, the testis or the ovary, the pancreas, the thyroid gland and the parathyroid gland of every one of the 10 dogs were examined, and none of these structures showed any effect attributable to TDE.

Morphologically, the condition in the adrenal gland of the dog has considerable resemblance to that observed in the adrenal gland of man in some instances of Addison's disease of the idiopathic or cytotoxic type, but we are not stressing either the morphologic resemblance or any idea of a specific chemical cause of the latter. The effect of TDE on the dog adrenal gland is, however, a striking example of chemical specificity in the causation of organic damage.

HEPATIC LESIONS PRODUCED BY LEAD IN RATS FED A HIGH FAT DIET

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ALL FORMS and degrees of damage of the liver have been described in lead poisoning: fatty infiltration or degeneration, hepatic cell degeneration with nuclear changes, fibrosis with lobular atrophy, and cirrhosis, among others.[1] Nevertheless, authors do not agree on the importance and the constancy of the hepatic injuries produced by lead.

In their book, Cantarow and Trumper [1b] concluded: "Despite the fact that hepatic cellular damage does not occur consistently in clinical or experimental lead poisoning, there seems little doubt that under certain conditions lead is at least able to contribute to the development of such damage which if protracted may eventuate in cirrhosis of the liver."

In 21 cases of acute lead poisoning in which the patients were children, Blackman [2] found inclusion bodies in the liver cells, many abnormal nuclei with or without inclusions, and occasional necrotic cells. In the majority of cases there was evidence of destruction of a few periportal liver cells together with slight chronic inflammatory reaction and scarring in each portal area. He also found somewhat similar hepatic lesions in rats given lead carbonate with drinking water.

On the other hand, rats fed a standard diet and poisoned during periods of three weeks to twenty-four months failed to show any conspicuous damage of the liver.[3]

The occurrence of hepatic lesions in lead-poisoned rats fed a high fat diet induced us to study the subject further. The results are presented in this paper.

From the Instituto de Biología y Medicina Experimental.

1. For a review of the literature see: (*a*) Schmidt, P.: Bleivergiftung, Berlin, Urban & Schwarzenberg, 1930; (*b*) Cantarow, A., and Trumper, M.: Lead Poisoning, Baltimore, Williams & Wilkins Company, 1944.

2. Blackman, S. S., Jr.: Bull. Johns Hopkins Hosp. **58**:384, 1936.

3. (*a*) Finner, L. L., and Calvery, H. O.: Arch. Path. **27**:433, 1939. (*b*) Fairhall, L. T., and Miller, J. W.: Pub. Health Rep. **56** (pt. 2):1610, 1941. (*c*) Chiodi, H.: Unpublished Data.

MATERIAL AND METHODS

White rats from our institute strain weighing 150 to 200 Gm. were fed twice a day through a rubber tube, no. 10, introduced down to the stomach. A 10 cc. B-D Sana Lock syringe was attached to the rubber tube and 7 to 15 cc. of the diet mixture was given each time, according to the animal's weight.

Lead poisoning was produced by giving daily, by stomach tube, 2 cc. of a 4.5 per cent lead acetate solution in distilled water slightly acidified with acetic acid.

Diets.—A high fat diet was fed to the rats, made up as follows: corn starch, 29 per cent; wheat flour, 20 per cent; casein, 10 per cent; McCollum's salt mixture,[4] 1 per cent; cod liver oil, 5 per cent; Mazola corn oil, 35 per cent. The total protein content was 14.7 per cent. To render the diet mixture more fluid, 70 cc. of tap water was added to each 100 Gm. of the diet.

The following materials were incorporated in the diet as further specified:

Choline chloride: 60 mg. per hundred cubic centimeters of the fluid diet, or about 10 to 12 mg. per rat, daily.

Inositol: Same as choline.

Tocopherols: 30 mg. of a tocopherols mixture (Parke-Davis) per hundred cubic centimeters of the fluid diet or not less than 3 mg. of alpha tocopherol to each rat, daily.

Dried brewers' yeast: 5 per cent at the expense of an equivalent amount of corn starch.

Casein: 30 per cent instead of 10 per cent at the expense of equivalent amounts of corn starch and wheat flour.

Methionine: 500 mg. per hundred cubic centimeters of fluid diet, or around 75 to 100 mg. per rat, daily.

Cysteine: Same as methionine.

A high carbohydrate diet consisted of: corn starch, 44 per cent; wheat flour, 40 per cent; casein, 10 per cent; cod liver oil, 5 per cent; McCollum's salt mixture, 1 per cent. Total protein content, 18.7 per cent.

Determination of Total Lipids and of Hemoglobin.—For total lipids the analytic procedure was similar to that employed by Handler[5]—two alcohol-ether extractions of ten minutes each, instead of one of five minutes, being made to insure that all lipids had been extracted. The phosphorus content of lipids was determined by the Fiske-Subbarow method. Phospholipids were calculated by assuming an average of 4 per cent phosphorus content.

Hemoglobin was determined with a Sahli-Hellige hemoglobinometer on blood obtained from the tail.

Microscopic Study.—Liver samples taken from the large left lobe were fixed in Zenker's solution as modified by Helly, Bouin-Hollande fluid[5a] and 4 per cent formaldehyde solution. Paraffin sections were stained with hemalum-eosin and

4. McCollum's salt mixture contains: sodium chloride, 146 Gm.; anhydrous magnesium sulfate, 225 Gm.; sodium biphosphate (sodium dihydrogen phosphate plus water), 293 Gm.; dipotassium hydrogen phosphate, 805 Gm.; tetrahydrogen calcium phosphate plus water, 456 Gm.; ferric citrate, 100 Gm.; calcium lactate, 1,098.5 Gm.

5. Handler, P.: J. Biol. Chem. **173**:295, 1948.

5a. Bouin-Hollande fixative fluid is made up as follows: copper acetate, 25 Gm.; trinitrophenol, 40 Gm.; formaldehyde solution (40 per cent), 100 cc.; distilled water, 1,000 cc.; acetic acid, 10 cc.

with Mallory's connective tissue stain as modified by Heidenhain (azocarmine G or B substituted for fuchsin). For reticulin and nuclei the Río Hortega method was used. Frozen sections were stained for fat with sudan III and hematoxylin.

RESULTS

Survival, General Condition and Body Weight.—The general condition of the rats fed the high fat diet was rather poor, gain of body weight being small or nil. Lead administered to these rats caused severe diarrhea, with a very poor general condition resulting; death followed within six to nineteen days (table). At autopsy an enormous dilatation of the stomach was found.

Choline added to the high fat diet did not prevent the symptoms or death caused by lead.

Rats fed the high fat diet with choline, inositol and yeast and poisoned with lead lived longer than those given lead which did not receive yeast. Nevertheless, only 1 rat of the former group survived more than thirty-eight days, as shown in the table. The general condition of these animals was good until a few days

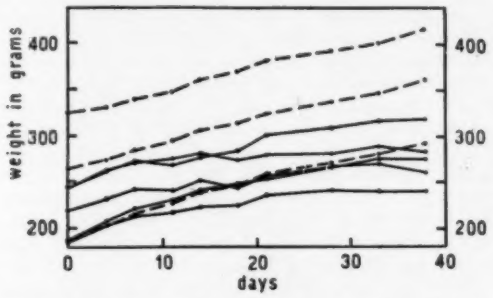

Fig. 1.—Growth curve of lead-poisoned (———) and control rats (.—.—.) fed the high fat diet with choline, inositol and yeast.

before death, at which time diarrhea and gastric dilatation appeared. Figure 1 shows that the animals which were given lead and the high fat diet with choline, inositol and yeast gained weight at a slightly lower rate than the controls. As between poisoned and control rats, weight differences were more conspicuous in those which did not receive yeast.

Controls fed the high fat diet with choline, inositol and yeast were in good condition at the end of the experiment; their weight gain was considerable, as shown in figure 1.

When methionine, cystine or 30 per cent of casein was added to the high fat diet with choline, inositol and yeast the whole intoxicated group survived throughout the experimental period. The general condition and the weight gain were the same as in the controls. If yeast was omitted from the diet, casein did not show any favorable effect on the life span of poisoned rats.

Animals fed the high carbohydrate diet, whether poisoned with lead or not, were in good health throughout the whole experimental period.

Hemoglobin.—Rats fed the high fat diet with choline, inositol and yeast showed a more severe anemia than that observed with a standard diet given ad libitum to

8 rats. In the first group (table) extreme values were 32 and 45 per cent (Sahli) and in the latter 58 and 74 per cent, poisoning period and doses being the same.

Controls given the high fat diet with choline, inositol and yeast showed normal values (table).

Casein did not modify the degree of the anemia. Methionine and cystine seemed to improve anemia slightly but, owing to our scanty experimental material, we could not reach any conclusion.

Liver.—High Fat Diet: The liver was enlarged in both poisoned and control rats, although more in the former, whether absolute weight or percentages of body weight were considered (table). In poisoned animals the liver was darker than normal, the edges being obtuse, but there was no change in the organ surface. Fat percentages were high in both groups, although more in controls than in lead-poisoned rats; phospholipids were low, as shown in the table.

Histologic examination showed an increase in size of the hepatic cells, with giant nuclei, in all the 9 poisoned rats. In 5 instances fatty infiltration or degeneration was present. Necrosis around the central vein of the lobule was found in 1 case.

In the controls there was fatty infiltration without any nuclear change.

High Fat Diet with Choline: In regard to liver changes the poisoned rats were rather similar to the preceding group, although fat content was lower (table). The liver of 1 rat weighed 16.2 Gm.; the average of the remaining 3 was 10.4 Gm.

It must be mentioned that only in 1 of the 4 intoxicated rats was the liver fat as high as 11.2 per cent; in the remaining 3 it ranged from 6.1 to 6.7 per cent. Phospholipids amounted to 23.6 per cent in the former and averaged 46.7 per cent in the latter.

Among controls given a high fat diet, the group receiving choline showed a clearcut decrease of the liver fat when compared with that not given choline.

In the lead-poisoned rats the liver showed giant nuclei as in the group not given choline, fatty lesions being present only in the single animal with a large liver.

High Fat Diet with Choline and 30 per Cent Casein: A mild fatty infiltration of the liver without any hypertrophy of the nuclei was found in poisoned animals; differences of liver size between control and intoxicated rats were small (table).

High Fat Diet with Choline and B Complex.[6]: In the poisoned rats the liver changes were similar to those found in the group fed the high fat diet with choline.

High Fat Diet with Choline, Inositol and Tocopherol: Microscopic study of 1 of the 3 poisoned rats showed giant nuclei in the hepatic cells without fatty infiltration.

High Fat Diet with Choline, Inositol and Yeast: Although there were differences of liver size between poisoned rats and controls in this group, they became smaller in the rats which survived fifty-two days.

Liver fat and phospholipid percentages were lower in rats given lead which survived thirty-eight days than in controls and only slightly higher than those found in poisoned rats fed the high carbohydrate diet (table). As expected, fat percentages were higher in the animals which lived longer.

Histologic examination of the livers of 7 rats of the poisoned group showed marked hypertrophy of the nuclei in 3 of them (fig. 2 *B* to *E*), less in the remaining ones. Mitotic figures were observed in 1 (fig. 2 *F*). There were foci of necrosis around the central vein of the lobule in 4 rats (fig. 2 *E*) and perilobular

6. Dissolved in 1.5 cc. of distilled water the rats were given pyridoxine, 0.06 mg.; riboflavine, 0.09 mg.; nicotinamide, 0.75 mg.; calcium pantothenate, 0.6 mg.; thiamine, 0.045 mg.; p-aminobenzoic acid, 3 mg.

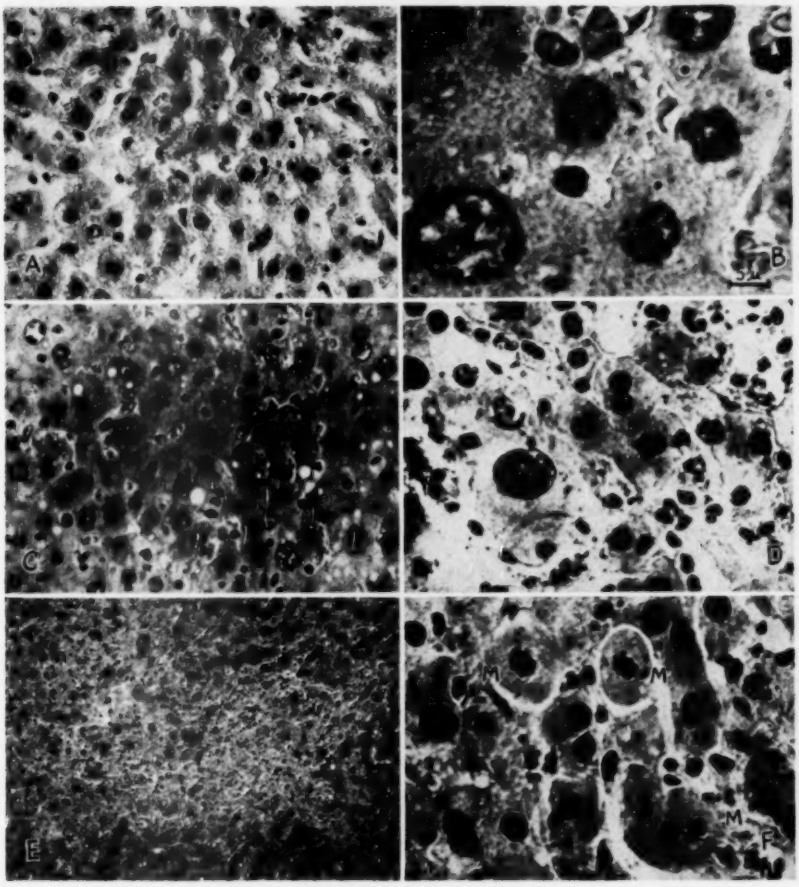

Fig. 2.—*A*, liver of control rat fed the high fat diet with choline, inositol and yeast during thirty-eight days. Hematoxylin-eosin; × 250.

B, higher magnification of part of *C*, showing a giant nucleus. Hematoxylin-eosin; × 643.

C, liver of lead-poisoned rat fed the high fat diet with choline, inositol and yeast during thirty-four days. Regeneration of the parenchyma and giant nuclei are shown. Hematoxylin-eosin; × 250.

D, hypertrophied cellula with a giant nucleus. Silver ammonium carbonate, Hortega's technic; × 428.

E, liver of lead-poisoned rat fed the high fat diet with choline, inositol and yeast during thirty-seven days. Centrolobular necrosis and hemorrhage are seen. Note some hypertrophied nuclei. Hematoxylin-eosin; × 128.

F, mitosis (*M*) of the hepatic cells of a rat treated with lead and fed the high fat diet with choline, inositol and yeast during twelve days. It was the only case in which mitotic figures were observed. Silver ammonium carbonate, Hortega's technic; × 428.5.

Results of Experiments

Lead-Poisoned Rats

Diet (Forced Feeding)	Rats	Sex	Days of Survival	Body Weight, Gm.	Liver: Weight, Gm.	Liver: Total Lipids, Percentage	Liver: Phospholipids, Percentage	Microscopic Lesions of Liver: Fatty Infiltration	Fatty Degeneration	Necrosis	Fibrosis	Nuclear Hypertrophy: +	Nuclear Hypertrophy: ++	Hemoglobin (Sahli), Percentage
High fat diet	9	♂	6-19	176	10.7	9.9 (2 rats)	34.0 (2 rats)	4	1	1	0	7	2	.....
High fat diet+choline	4	♀	3-9	170	11.8	8.8 (4 rats)	35.1 (4 rats)	0	1	0	0	0	4	.....
High fat diet+choline+B complex	3	♀	12-18	190	10.1	.....	.....	1	0	1	0	1	2	.....
High fat diet+choline+inositol+tocopherol	5	♀	3-8	198	....	.....	.....	0	0	0	0	0	1†	.....
High fat diet+choline+inositol+yeast	5	♂	20-29	253	....	.....	.....	..	..	..	..	..	..	.....
High fat diet+choline+inositol+yeast	3	♀	15-34	184	11.7	.....	.....	2	0	0	3	1	2	35-73
High fat diet+choline+inositol+yeast	3	♂	31-38	266	12.5	7.4 (3 rats)	41.6 (3 rats)	0	0	3	0	2	1	22-45
High fat diet+choline+inositol+yeast	1	♂	52	323	12.3	9.4 (1 rat)	30.1 (1 rat)	0	0	1	0	1	0	
High fat diet+choline+inositol+yeast+casein ‡	7	♂	34 *	314	13.9	6.5 (5 rats)	55.8 (5 rats)	4	0	0	1	2	0	29-68
High fat diet+choline+inositol+yeast+methionine	3	♀	33 *	265	10.7	.....	.....	0	0	3	0	1	0	46-68
High fat diet+choline+inositol+yeast+cystine	4	♂	32 *	296	13.2	.....	.....	4	0	3	0	4	0	46-65
High fat diet+choline+casein ‡	3	♂	8-23	237	12.8	.....	.....	3	0	1	0	0	0	33-56
High fat diet+choline+inositol+casein ‡	5	♂	8-14	260	....	.....	.....	..	..	..	..	..	..	.....
High carbohydrate diet	6	♂	46 *	215	9.4	6.5 (4 rats)	45.9 (4 rats)	0	0	0	0	1§	0	.....
Controls														
High fat diet	7	♂	19 *	172	8.4	13.7 (4 rats)	25.0 (2 rats)	5	1	0	0	0	0	.....
High fat diet+choline	1	♀	28 *	205	10.1	9.0 (1 rat)	.....	1	0	0	0	0	0	.....
High fat diet+choline+B complex	2	♀	23 *	207	10.1	.....	.....	2	0	0	0	0	0	.....
High fat diet+choline+inositol+tocopherol	4	♀	8 *	207	....	.....	.....	..	..	..	..	..	..	.....
High fat diet+choline+inositol+yeast	2	♂	30 *	272	....	.....	.....	..	..	..	..	..	..	.....
High fat diet+choline+inositol+yeast	3	♀	34 *	233	9.2	.....	.....	0	0	0	0	0	0	73-94
High fat diet+choline+inositol+yeast	1	♂	38 *	292	10.2	9.0 (1 rat)	.....	0	0	0	0	0	0	96-100
High fat diet+choline+inositol+yeast	2	♂	52 *	445	13.8	10.1 (2 rats)	28.3 (2 rats)	0	0	0	0	0	0	
High fat diet+choline+inositol+yeast+casein ‡	5	♂	34 *	301	12.0	6.1 (3 rats)	50.2 (3 rats)	4	0	0	1	0	0	80-97
High fat diet+choline+inositol+yeast+methionine	1	♀	33 *	282	10.6	.....	.....	0	0	0	0	0	0	97
High fat diet+choline+inositol+yeast+cystine	3	♂	32 *	338	14.1	.....	.....	2	0	1	0	0	0	93-97
High fat diet+choline+casein ‡	2	♂	23 *	231	11.4	.....	.....	0	0	0	0	0	0	63-88
High fat diet+choline+inositol+casein ‡	1	♂	14 *	271	....	.....	.....	..	..	..	..	..	..	.....
High carbohydrate diet	4	♂	46 *	207	7.7	7.0 (4 rats)	45.2 (4 rats)	0	0	0	0	0	0	.....

* The rats were killed with illuminating gas.
† A microscopic study was made of 1 rat only.
‡ This diet contained 30 per cent casein instead of 10 per cent.
§ Very slight hypertrophy was noted.

fibrosis with derangement of the parenchyma and trabeculae in another 4. Slight fatty infiltration was observed in 2 poisoned rats but in none of the controls (fig. 2*A*).

High Fat Diet with Choline, Inositol, Yeast and 30 per Cent Casein: The liver weights of the poisoned rats were not increased whether expressed as absolute values or as percentages of the body weight (table).

Nuclear hypertrophy was present in the liver of 2 of the 6 intoxicated animals which were examined. The hepatic parenchyma was normal except in 1 case in which perilobular sclerosis was found.

In controls, hepatic cells were infiltrated with tiny droplets of fat, and periportal fibrosis and proliferation of the bile ducts were present.

High Fat Diet with Yeast, Given ad Libitum: Lead-poisoned animals receiving this diet diminished their daily intake of food, lost body weight and died in sixty to seventy-five days. The livers of the 5 poisoned rats showed hypertrophy of the nuclei of the hepatic cells, without fatty infiltration, which was present in 1 of 3 controls receiving the same diet.

High Fat Diet with Choline, Inositol, Yeast and Methionine: There was no difference in size of liver between poisoned rats and controls (table). One of the 3 poisoned rats showed slight nuclear hypertrophy, and small foci of necrosis of the central part of the lobule were present in all. In controls the hepatic parenchyma was normal.

High Fat Diet with Choline, Inositol, Yeast and Cystine: There were small foci of necrosis around the central vein of the lobule, edema and hemorrhagic foci in both control and poisoned rats. In the latter there was also mild nuclear hypertrophy.

High Carbohydrate Diet, Low in Fat: The livers of lead-poisoned rats were slightly heavier than those of controls. The fat and phospholipid percentages can be considered within normal limits for a diet rather low in choline and without yeast (table).

In 1 of the 5 poisoned animals there was slight hypertrophy of hepatic nuclei, and glycogen infiltration of the parenchyma was present in 3 of them.

Nuclear Lesions.—There was hypertrophy of the nuclei of the hepatic cells, mostly located around the center of the lobule, the cells being also enlarged. There was a loss of the characteristic radial arrangement of the columns of hepatic cells. Diameters of the hypertrophied nuclei were quite outside normal limits (upper limit, 15 to 16 microns instead of 6 to 8 microns, as shown in fig. 2*B*). Giant nuclei showed the chromatin irregularly distributed in granules or in a thick net (prophase), one, two or sometimes more acidophilic nucleoli being present. In some cases one or more vacuoles filled the nucleus almost completely. There were also cells which were devoid of nuclei. Binucleated cells were present in larger number in lead-poisoned livers than in those of controls.

It must be noted that in none of the examined livers were clear macroscopic signs of fibrosis or necrosis found.

COMMENT

When lead acetate was given to rats forcedly fed a high fat diet, severe hepatic damage and anemia developed consistently, and the animals died within three to eighteen days. The addition of choline or inositol to the high fat diet did not lengthen the time of survival. When yeast was included in the diet, rats survived longer, though only by exception more than thirty-eight days.

If the high fat diet with yeast was fed ad libitum to the poisoned rats, there was a diminution in their daily intake of food, which resulted in a slow process of undernutrition and finally in death after sixty to seventy-five days.

By increasing to 30 per cent the casein content of the high fat diet with choline, inositol and yeast, the death of poisoned animals was prevented within an experimental period of thirty-four days. If yeast was omitted, casein had no effect on the time of survival.

That death of rats receiving lead was caused by overfeeding of fat is shown by the fact that a high carbohydrate diet low in fat allowed poisoned rats to survive in good health for at least forty-six days. Likewise, rats kept on a standard diet and receiving similar doses of lead remained alive for one year.[6a]

Increase in the size of the liver in the rats receiving lead and a high fat diet was independent, partially at least, of the fatty infiltration of the organ, since it was observed in cases in which the latter was not present.

It might be thought that the hepatic lesions could be due only to a high fat content or a protein deficiency of the diet, but the fact that such lesions were not present in the controls fed the same diet allows us to discard such an assumption. A further proof is given by the observation that the lesions characteristic of lead poisoning were present even in those cases in which fatty infiltrations or degeneration was completely prevented by lipotropic agents and yeast or tocopherol.

Increasing the protein content of the diet to 30 per cent prevented hepatic damage from lead in most of the rats. Methionine was somewhat less active, and cystine almost inactive. Yeast was not necessary for the preventive action of casein but was necessary for the prevention of death of the lead-poisoned rats.

Lead acetate given without an excess of fat did not produce conspicuous hepatic damage, as found in the rats fed a high carbohydrate diet low in fat or in those fed a standard diet ad libitum and poisoned daily during three months with 2 cc. of 12 per cent lead acetate solution.[8c] The lack of damage of the liver may be explained by a low hepatic storage of lead[7]; administration of fat would increase the lead storage, as found in rabbits by Weyrauch and Necke.[8] The damage caused by lead is thus very similar to that caused by trinitrotoluene, which produces injuries of the liver only when the rats are restricted to a high fat diet.[9]

6a. Chiodi, H., and Sammartino, R. A.: Nature, London **160**:680, 1947.

7. Laug, E. P., and Harris, H. P.: J. Pharmacol. & Exper. Therap. **64**:388, 1938.

8. Weyrauch, F., and Necke, A.: Ztschr. f. Hyg. u. Infektionskr. **114**:629, 1933.

9. Himsworth, H. P., and Glynn, L. E.: Clin. Sc. **4**:421, 1939-1942.

The increased waste of proteins occurring in lead poisoning,[10] particularly of sulfur-containing proteins, perhaps exaggerated by fat overfeeding, could produce a protein deficiency, which in turn would be the origin of the hepatic damage described in our rats. The preventive action of casein and methionine speaks in favor of such a hypothesis.

According to Hammet,[11] quoted by Cantarow and Trumper,[1b] the retardation of the growth rate of roots and chick embryos produced by lead is due to suppression of cell proliferation, mitotic nuclei apparently showing the greatest affinity for the toxic elements, which was also found in the nuclei and walls of other cells. This author concludes that lead enters into combination with an organic sulfhydryl compound analogous to glutathione, if not this compound itself. However, Vannucci [12] found an increase of the reduced glutathione in the liver of lead-poisoned guinea pigs.

Later studies confirmed the toxic effect of lead on mitosis.[13]

Another thing in favor of the belief that lead exerts a specific action on cellular differentiation and division is the fact that giant nuclei are present in the cells of the renal tubules of the rats [3c] and the nuclear changes occur in the erythropoietic cells of the bone marrow of the dogs [3c] poisoned with lead.

Therefore, lead would retard or inhibit, partially at least, the mitosis of hepatic cells, which, being unable to undergo division, would continue to grow, becoming very large or even giant cells. This abnormal cellular growth would explain the increase in the weight of the organ found by us. A similar mechanism has been made responsible for the increase of the size of the kidneys in lead poisoning.[3a]

In favor of the mitosis-inhibiting action of lead stands the fact that except in 1 case mitosis was rarely seen even in livers which showed the utmost nuclear hypertrophy. Dawson's statement [14] that changes in the size and the number of the nuclei of mammals' liver cells would arise from a variable degree of failure of mitosis points in the same direction.

In brief, it appears that when rats fed a high fat diet are poisoned with lead, there is an abnormal inhibition or waste of sulfhydryl-containing proteins of the hepatic cells, which disturbs the enzymatic processes of mitosis. When the toxic injury is not severe, it retards or partially inhibits the mitosis of a number of cells, which continue to grow until

10. Terroine, T.: Trav. Soc. chim. biol. **26**:1179, 1944.

11. Hammet, F. S.: Protoplasma **4**:187, 1928; **5**:135, 187, 535 and 547, 1929; cited by Cantarow and Trumper.[1b]

12. Vannucci, F.: Giordi clin. med. **14**:585, 1933.

13. Levan, A.: Nature, London **156**:751, 1945 Mangenot, G., and Carpenter, S.: Compt. Rend. Soc. de biol. **139**:268, 1945.

14. Dawson, A. B.: Anat. Rec. **102**:393, 1948.

the inhibition is overcome or until the too large size of the cells interferes with the metabolic process. In other cells the toxic action, being too severe, causes cell death, producing foci of necrosis and afterward fibrosis if the animal survives long enough. Casein and methionine compensate the losses of sulfhydryl-containing proteins caused by lead and prevent the toxic injuries of the liver.

It is worth mentioning the recent work of Orr and Price,[15] who found that para-dimethylaminoazobenzene, a carcinogenetic agent, when given to rats in large doses produces hepatic lesions similar to those described in this paper.

SUMMARY AND CONCLUSIONS

Rats forcedly fed a diet containing 40 per cent fat were given daily 2 cc. of a 4.5 per cent lead acetate solution. Death followed within six to nineteen days and the livers showed cellular and nuclear hypertrophy, fatty infiltration or degeneration and necrosis. Addition of choline, inositol, tocopherol and brewers' yeast prevented fatty infiltration or degeneration in most of the animals, but not cellular and nuclear hypertrophy and necrosis.

Casein and, to a smaller degree, methionine prevented cellular and nuclear hypertrophy and necrosis of the liver when added to the high fat diet with lipotropic agents in the presence or the absence of yeast.

Lead acetate given without an excess of fat did not produce conspicuous hepatic damage or the death of the rats within the experimental period.

Casein prevented the death of the animals poisoned with lead and fed the high fat diet within the experimental period only when yeast was present in the diet.

Possible mechanisms of the nuclear changes are discussed.

15. Orr, J. W., and Price, D. E.: J. Path. & Bact. **60**:461, 1948.

CARDIAC HYPERTROPHY IN EXPERIMENTAL ARTERIOVENOUS FISTULA

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AND
HUGH BRAWNER
DURHAM, N. C.

THE PATHOPHYSIOLOGIC and the clinical picture of arteriovenous fistula have been extensively studied.[1] This report is devoted to studies of the effects of experimental arteriovenous fistula on canine heart muscle. Interest is centered about three problems which may be stated as follows: 1. To what degree does the heart hypertrophy? 2. Does the hypertrophied heart return to normal after elimination of the overload (excision of fistula)? 3. Does an arteriovenous fistula of short duration (five to seven days) produce cardiac hypertrophy?

EXPERIMENTAL PROCEDURE

A fistula was established between the common carotid artery and the external jugular vein in 11 large dogs (11 to 16 Kg.). The incisions in the vessels were 2.5 to 3.5 cm. in length, and the edges were sutured with fine silk (atraumatic eye suture size 6-0). The suture technic of Deterling [2] was used, and emphasis was laid on careful stripping of the adventitia to prevent clotting. For the same reason, the intimal surface of the fistula was coated with a few drops of sterile liquid petrolatum U. S. P. (Carrel [3]). All the fistulas remained patent, and thrombosis was never encountered despite the fact that anticoagulants were not used. The arteriovenous shunt was made as large as possible in order to produce, it was hoped, a pronounced and rapid effect on the heart muscle. The choice of the vessels of the neck was indicated by their size and accessibility. Whether the effect of an arteriovenous fistula of these vessels may be influenced by the nearby carotid sinus is unknown.

The effect on heart muscle was measured by weighing the heart according to the method of Herrmann.[4] The weight of the cleaned and fixed left and right ventricles devoid of fat, pericardium, vessels and valvular ring was deter-

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1. (*a*) Gauer, O., and Linder, F.: Klin. Wchnschr. **26**:1, 1948. (*b*) Holman, E.: Arteriovenous Aneurysm, New York, The Macmillan Company, 1937; (*c*) Surgery **8**:362, 1940; (*d*) Ann. Surg. **112**:840, 1940; (*e*) **124**:920, 1946.

2. Deterling, R. A.: Surgery **18**:679, 1945.

3. Carrel, A.: Bull. Johns Hopkins Hosp. **18**:18, 1907.

4. Herrmann, G. R.: Am. Heart J. **1**:213, 1925-1926.

mined. Reference is made throughout this paper to the ratio of the weight of the cleaned and fixed ventricles × 100 to the body weight (VW/BW ratio).

Changes in the size of the heart were followed by lateral roentgenograms of the chest taken at a distance of 91.5 cm. (36 inches).

RESULTS

Effect of a Fistula of Long Standing.—The first series comprises 3 dogs in which fistulas were established, respectively, for 87, 88 and 93 days. Their VW/BW ratios are 0.811, 0.698 and 0.872.

Effect of a Fistula of Short Duration.—Eyster [5] rejected the concept of physiologic work hypertrophy and suggested that cardiac enlargement is a form of injury hypertrophy, brought about by abnormal stretching of the muscle fibers in the initial period of overload (foci of hydropic degeneration, necrosis, etc.). In one series of dogs he constricted the aorta ascendens for a period of 3 to 6 days.

TABLE 1.—*Synopsis of the Experimental Data*

Dog	Final Weight, Kg.	Lived with Fistula, Days	Lived after Excision of Fistula Days	Weight of Cleaned + Fixed Ventricles, Gm.	C+F.V.W.×100 / B.W.
Series 1					
a	10.43	93	..	91.0	0.872
b	12.70	87	..	103.0	0.811
c	14.52	88	..	101.3	0.698
Series 2					
d	14.17	5	105	82.8	0.584
e	12.93	5	107	77.5	0.599
f	14.06	7	104	82.6	0.587
Series 3					
g	12.84	77	112	79.1	0.616
h	17.12	73	69	104.1	0.608
i	13.72	80	62	105.0	0.765
k	12.36	67	70	80.7	0.652
l	14.62	73	67	99.5	0.680

To another series he gave massive transfusions, rapidly increasing the total blood volume up to 175 to 200 per cent. Cardiac hypertrophy, determined by roentgenologic observation and terminal heart weight, developed in these dogs. Eyster concluded that the most important factor leading to cardiac hypertrophy is not increased work of the muscle per se but injury of the muscle and the reaction to that injury.

Paralleling his work, we established arteriovenous fistulas in the necks of 3 dogs and excised them after 5, 5 and 7 days. The dogs were killed 105, 107 and 104 days after the excision and showed VW/BW ratios of 0.584, 0.599 and 0.587, respectively.

Effect of the Removal of a Fistula of Long Duration.—The third series comprises 5 dogs who had arteriovenous fistulas for 67, 72, 73, 77 and 80 days and were kept alive for 70, 69, 67, 112 and 62 days after the excision of the fistulas. Their VW/BW ratios are 0.652, 0.608, 0.680, 0.616 and 0.765.

5. Eyster, J. A. E.: (*a*) Tr. A. Am. Physicians **42**:15, 1927; (*b*) J. A. M. A. **91**:1881, 1928.

COMMENT

Our findings have been compared with the "standard" values determined by Herrmann [4] on 200 apparently healthy, normal dogs. These, however, were not examined for hypertension or renal disease. Herrmann's table reveals an increasing range of variation of ratios with increasing body weight. This distribution is probably in part due to the somatic differences of the various breeds making up the total. (Rabbits show more constant ratios.[6])

The results of our roentgenologic studies could not be correlated with the heart weights, and it appears that our method is inadequate.

In contrast to our series 1, Drury and Wightman [7] succeeded in producing cardiac hypertrophy within 3 months (increase in weight of from 45 to 125 per cent). This was accomplished in rabbits by means of carotid-jugular fistulas. As may be seen in the chart, 2 dogs of series 1 showed VW/BW ratios at the upper limit of normal; one of the ratios was slightly above the average. None exceeded the range of normal established by the 200 dogs of Herrmann. This holds true regardless of what body weight we choose. Some of our experimental animals lost weight, in part due to depressive anorexia. The final live weight was used; the ratios are thus weighted in some of the dogs in the direction of hypertrophy. This part of the experiment permits no positive conclusions. The following suggestions and interpretations are, however, drawn from our experience:

1. The arteriovenous shunts either were not large enough for the size of the animals or did not function long enough to produce clearcut hypertrophy, or both.

2. Dogs may compensate the additional circulatory load more efficiently than rabbits.[8]

The results noted in series 2 do not confirm Eyster's [5b] work. The VW/BW ratios are slightly below average and well within normal limits, indicating complete absence of hypertrophy (see chart). This, however, does not necessarily invalidate Eyster's work, since our experimental method may not produce sufficient overwork to result in cardiac hypertrophy. For example, if Eyster's findings are correct, our inability to duplicate his results may be due to too small a fistula, resulting in too gradual an increase in blood volume and cardiac output. Since, according to Eyster, the time factor is of prime importance, a small

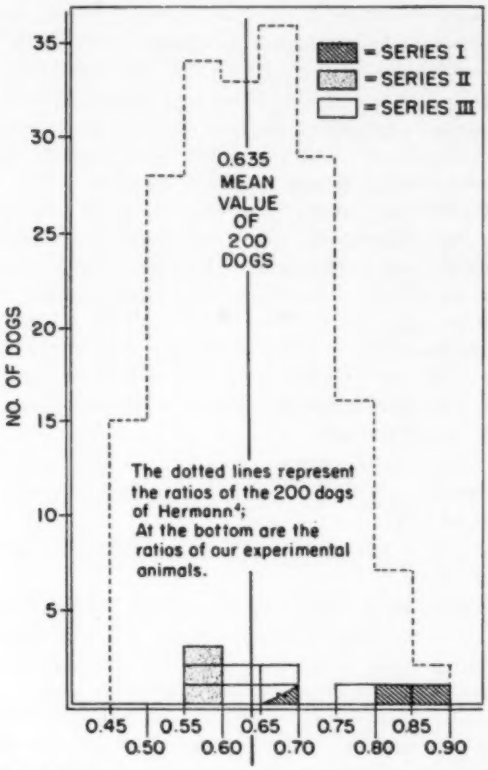
6. Joseph, D. R.: J. Exper. Med. **10**:521, 1908. Eyster.[5b]

7. Drury, A. N., and Wightman, K. J. R.: Quart. J. Exper. Physiol. **30**:45, 1940. Drury, A. N.: ibid. **33**:107, 1945.

8. Ghetti, L.: Chirurg. **2**:20, 1947; abstracted, Internat. Abstr. Surg. **86**:59, 1948. Drury and Wightman.[7]

arteriovenous fistula could not effect injury of the myocardial fibers. It would appear that a fair test of his results could be achieved by the production of an aorta–vena cava fistula of a size and a site which barely permit the dog to survive the procedure.[1d]

Dog i of the third series has a rather high VW/BW ratio. (This animal suffered from pronounced depressive anorexia, and the ratio in



Ratios of weight of cleaned and fixed ventricles × 100 to body weight, compared with Herrmann's [4] range of normal ratios.

our opinion reflects marked loss of weight rather than hypertrophy.) With this exception (dog i) the ratios are fairly well grouped about the average value, indicating possibly a return to normal of slightly hypertrophied hearts. (This course of events has been conclusively demonstrated in rabbits.[4]) The heart of dog h had 6 adult heart worms

(Dirofilaria immitis) floating in the ventricles. Their effect on the cardiac function was apparently nil, since the VW/BW ratio is close to the average value. This dog showed a slight gain in weight.

SUMMARY

An arteriovenous fistula was established between the large cervical vessels in dogs for studying the possibility that the hypertrophied heart may return to normal size after reestablishment of the normal circulation. In dogs with this type of fistula which were maintained for 3 months and then killed, no significant hypertrophy of the heart was found. The hearts of dogs in which the fistula was allowed to remain for 2½ months and which survived its excision for an additional 2 months did not vary in weight from the normal.

VENOUS ATHEROMA

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ABNORMAL thickenings of the venous wall, although not as intensively studied as the corresponding lesions of arteries, have received some sporadic attention. As in the case of "arteriosclerosis," the term "phlebosclerosis" has come to cover a multitude of lesions. The thickenings may be focal or diffuse; they may involve one or two or, more often, all three coats of the vein, and they may consist of pathologic material or merely of hyperplastic normal constituents of the vessel.

The condition called venofibrosis [1] is a bilateral symmetric thickening without dilatation of superficial and deep veins due to extensive fibrosis of the media with some irregular thickening of the intima. No calcium or fat was ever seen in these lesions.

Another type of venous thickening has been observed in the portal veins and inferior vena cava in cases of hepatic cirrhosis and congestive cardiac failure.[2] It consists in intimal hyperplasia and muscle appearing in the subendothelial layer, medial hypertrophy of the portal veins and adventitial hypertrophy of the inferior vena cava. Some of the hypertrophied muscle is replaced at a later stage by fibrous tissue. Fat has not been demonstrated.

The increased venous pressure of congestive cardiac failure causes similar adaptive, and later degenerative, change in the hepatic veins [3] and in the superior vena cava.[4] In these cases, also, fat was never found in the lesions.

A considerable literature has sprung up about the changes found in the splenic vein in Banti's syndrome and in the portal vein and its tributaries in hepatic cirrhosis, but only in a single case has fatty intimal change been observed.

The same applies to the pulmonary veins. While phlebosclerosis is not uncommon in these vessels in cases of mitral stenosis,[5] there is

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1. Hauswirth, L., and Eisenberg, A. A.: Arch. Path. **11**:857, 1931.
2. Pei-Lin, Li.: J. Path. & Bact. **50**:121, 1940.
3. Gross, H.: Arch. Path. **23**:457, 1937.
4. Gross, H., and Handler, B. J.: Arch. Path. **28**:22, 1939.
5. Ljungdahl, M.: Untersuchungen ueber die Arteriosklerose des kleinen Kreislaufs, Wiesbaden, F. G. Bergmann, 1915.

again only 1 isolated instance in literature of fatty degeneration of the pulmonary vein.[6]

If a vein is placed under increased tension by the formation of an arteriovenous fistula, very similar changes occur. "The wall of the involved vein becomes thickened and hypertrophied. In addition there is usually a very marked deposition of calcium in the rim of the fistula." [7]

Equally, if a venous segment is transplanted into the arterial circulation great hyperplasia of all coats takes place, leading sometimes to obliteration of the lumen. At other times irregular intimal thickenings have been described.[8] This subject was reported on by Carrel [9] on various occasions, but neither he nor other observers ever found any fat in the intimal thickenings.

Finally one might mention that Tedeschi [10] observed local fibromuscular thickening in the walls of veins adjacent to arteries, rendering the adjacent side of the vein twice as thick as the opposite side. The thickening was largely due to adventitial hyperplasia.

In conclusion it can be stated that every chronic increase of venous pressure leads to thickenings of the veins involved and finally to degenerative changes. Another striking fact which a survey of the literature brings out is the monotonous unanimity with which authors repeat the statement that they were unable to find fat in the phlebosclerotic lesions. These statements need not always be taken at their face value, for in many papers it is apparent from the description of the technic employed that no attempt was made to find fat (e. g., Watts [8] and Gross [2]). On the other hand, there is no doubt that most of these lesions do not in fact contain fat, so that reports referring to fatty degeneration of the intima of veins can be counted on the fingers of one hand. Orth [11] seems to have seen it in the pulmonary veins in mitral stenosis. Benda expressed himself on the subject thus: "I must confess, that I have looked for these intimal fatty changes . . . in vain, the only specimen . . . which I have seen . . . appears to me to be isolated in the literature." He went on, however, to mention intimal fatty change of varicose veins and of the portal vein and reproduced a picture of atherosclerosis occurring in a pial vein of a spinal angioma.[6] Fat is, of course, quite frequently found in organized mural thrombi.

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6. Benda, C., in Henke, F., and Lubarsch, O.: Handbuch der Speziellen Pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2.

7. Reid, M. R.: Am. J. Surg. **14**:17, 1931.

8. Watts, S. H.: Bull. Johns Hopkins Hosp. **18**:153, 1907.

9. Carrel, A., and Guthrie, C. C.: Compt. rend. Soc. de biol. **59**:412 and 596, 1905; **60**:529, 1906. Carrel, A.: Bull. Johns Hopkins Hosp. **18**:12, 1907.

10. Tedeschi, C.: Anat. Rec. **79**:243, 1941.

11. Orth, cited by Benda.[6]

It can be said therefore that while pathologic thickening of veins is a well recognized phenomenon, venous atheroma, i. e., fatty infiltration of the intima of veins with subsequent fibrosis, hyalinization or calcification, remained a pathologic curiosity up to 1926 when Schilling [12] published his analysis of a lesion which occurs at the origin of the inferior vena cava and which had been noticed by Cramer [13] in 1921. This lesion Schilling encountered in 50 per cent of all postmortem examinations, and his histologic study of 100 of these plaques revealed fat either alone or associated with hyaline material or calcium in 49 of them. In every other respect the lesions resembled arterial atheroma. Schilling's paper should have received more attention than it did. If true atherosclerosis occurs with great regularity in a certain fixed location in the venous system, this fact may throw light on the causes of atheroma. The purpose of this paper is to add to Schilling's findings and to stress the significance of his discovery.

MATERIAL

In the course of an investigation of atheroma aortae,[14] yellowish plaques were noted to occur with considerable frequency about the origin of the inferior vena cava. It was decided to study the nature of these lesions. In this paper is presented an analysis of 245 cases. They represent an almost unbroken series of all the autopsies at the Royal Infirmary Edinburgh from the beginning of December 1947 to the end of May 1948. There has been no selection other than that introduced by the nature of the hospital, viz., that there are few patients below the age of 12 and few patients with contagious disease. In the majority of instances the inferior vena cava was available only from the renal level downward, i. e., about 2 inches (5 cm.) of it. In a few cases only the first inch of the vessel was obtained; in other cases the whole subdiaphragmatic length of the vessel could be secured. Together with this lower part of the inferior vena cava were removed in each case the two common iliac veins and the abdominal portion of the aorta with the iliac arteries, to which the veins remained attached. It was found advisable to remove the veins unopened and subsequently to open them from the back, as thereby a better idea of the topography was obtained. The necessity of severing the right common iliac artery in order to open the left common iliac vein was thereby obviated. The specimens were fixed in 4 per cent formaldehyde solution.

The lesions consisted of white or yellow plaques up to 0.5 cm. square or streaks up to 2.5 cm. in length. In some instances a fairly large area, instead of showing these smooth lesions, was roughened and exhibited a yellowish granularity covering the smooth intima. The plaques were slightly raised and looked much like the nodules of mild arterial atheroma. They occurred in a strictly limited area of the

12. Schilling, W.: Virchows Arch. f. path. anat. **262**:658, 1926.
13. Cramer, H.: Virchows Arch. f. path. Anat. **130**:46, 1921.
14. Geiringer, E.: Brit. J. Soc. Med. **2**:132, 1948.

venous surface which was available for inspection, viz., at and about the orifice by which the left common iliac vein joins the inferior vena cava and in a 2 cm. upward prolongation of the line of this orifice (figure).

The plaque-bearing area lay in that part of the vein which is situated entirely behind the aorta and the right common iliac artery. In addition to the proximal end of the left common iliac vein it comprised the lowest 2 cm. of the inferior vena cava, which is the only part

Abdominal aorta, lower third of inferior vena cava and iliac vessels. The veins have been opened from the back to display the venous plaque in its typical location in the center of the anterior part of the ostium by which the left common iliac vein joins the inferior vena cava. R.C.I.V. indicates the right common iliac vein.

of this vessel which lies entirely behind the aorta, to which it is fixed in this situation. Posteriorly the plaque-bearing area was in relation with the prevertebral fascia, which in this region is usually thin and closely adapted to the front of the lower lumbar region of the spine. For practical purposes the plaque-bearing area of the inferior vena cava and iliac vein is that portion of these vessels which lies between the last lumbar vertebrae at the back and the bifurcation of the aorta

in front. In no other part of the venous surface under investigation were such plaques ever found. In 8 instances gross calcification of the plaques was noted. In no instance was it possible to squeeze atheromatous material from the lesions, nor was there any macroscopic evidence of ulceration. Of peculiar interest is a case in which there was sinistroposition of the inferior vena cava. On examination of the venous bifurcation a patch of sclerosis was found in the region of the orifice of the *right* common iliac vein, i. e., where in this instance the left common iliac artery crossed the vessel.

These findings are in good agreement with those of Schilling, who said that the lesion is usually found "in the middle part of the posterior caval wall shortly above the confluence." [15] The illustration which accompanies Schilling's paper makes it, moreover, certain that he was describing the same lesions.

HISTOLOGIC ASPECTS

Frozen sections were prepared from 11 specimens showing the lesion, as well as from some normal-looking veins and from some veins showing the diffuse thickening which is so constant a feature in cases of chronic congestive cardiac failure. The sections were stained with scarlet red or sudan III and variously counterstained.

The normal inferior vena cava does not possess a subendothelial layer. In both the arteries and the veins of the newborn the endothelium comes to lie directly on the internal elastic lamina. Connective tissue, intervening between these two layers, is soon formed in the larger arteries, but the veins throughout life remain normally devoid of such a subendothelial layer. In a normal vein the very soil on which atheroma grows is missing. However, in the course of life in many people the inferior vena cava acquires such a subendothelial layer, and this acquisition is constantly found in persons who exhibit increased venous pressure from whatever cause.[16]

This fact, viz., that the subendothelial layer in which the sclerotic plaque occurs, is not found in normal veins, raises the question whether the plaque is secondarily implanted on an already hypertrophied intima or whether the formation of the subendothelial layer proceeds *pari passu* with the formation of the plaque. In this series both types of occur-

15. A slight misconception has crept into this, probably due to the fact that Schilling opened his veins completely before looking at the lesions. In the completely opened veins the upper part of the orifice of the left common iliac vein appears as part of the inferior vena cava and one is tempted to call inferior vena cava what is in reality still left common iliac vein. The most common and very often the only place at which these plaques are found is in fact the orifice of the left common iliac vein.

16. Dijkstra, O. H.: Nederl. tijdschr. v. geneesk. **76**:2423, 1932. Pei-Lin.[2]

rence were noted. In some cases the plaque occurred in a vein already diffusely hypertrophied and possessing a subendothelial layer; in other cases one could see that the vein above and below the lesion was normal, i. e., devoid of such a layer. In the latter cases it must be assumed that the local subendothelial thickening and the atheroma formation are part of the same process. Indeed, in 5 of the 11 cases the plaque was entirely composed of fibrous elastic and muscular tissue, so that it represented no more than an exaggerated and strictly localized diffuse intimal hyperplasia of the type met with in cases of increased venous pressure. The media in these cases was either normal or atrophied, while the adventitia was usually considerably hypertrophied. These findings correspond with those in the aforementioned diffuse thickenings of the inferior vena cava. The amount of smooth muscle is variable in these connective tissue plaques, and in 2 instances there was evidence of hyalinization. The elastica was often split, with the plaque occurring between the reduplicated layers. This is stressed by Jores [17] as a feature of true arteriosclerosis. Of the 100 cases of Schilling, 30 showed this purely connective tissue composition.

The main question, however, was whether it would be possible to confirm Schilling's results respecting the fat content of these lesions. He had found fat in 49 of 100 cases, either alone or in combination with hyalinization, calcification or both; in 5 of our 11 cases the lesions were found to contain fat. The fat was seen in small droplets finely distributed between the connective tissue cells and fibers. It tended to occur toward the center of the plaque or in the depth toward the media, and in 1 case it was seen to penetrate for a short distance between the muscle cells of the media. Gross conglomerations of fat, cholesterol crystals or typical "foam cells" were not encountered, but small connective tissue cells containing granular fat were numerous in some sections. In 1 case there was partial calcification of the plaque, the picture being similar to that of calcified foci in atheromatous plaques in small arteries. The central core of calcium was surrounded by many small extracellular granules of calcium and droplets of fat suggesting that a calcific metamorphosis of a lipoid focus had taken place. In another case small groups of round cells occupied tissue spaces here and there in all three layers of the vessel. Apart from this there was not in any of the cases an appearance suggestive of inflammation.

All these findings agree well with the results of Schilling and fully confirm his most significant discovery that almost half of these intimal thickenings contain intracellular and extracellular fat. In all other essential respects, also, these lesions agree with atheroma, being differ-

17. Jores, L.: Wesen und Entwickelung der Arteriosklerose, Wiesbaden, J. F. Bergmann, 1903.

ent from arterial atheroma in degree only. While in arterial lesions fat may predominate over connective tissue, venous atheroma shows the inverse relation. While the fat infiltrations of arterial atheroma tend to coalesce, the fat droplets of the venous intima remain discrete, although in 1 specimen some coalescence can be observed. Splitting of the elastica is a prominent feature in both types of lesion. One may thus regard these venous lesions as mild atheroma with a marked tendency to heal by fibrosis.

In conclusion I wish to draw attention to the unbroken series of histologic pictures leading from the normal inferior vena cava to the atherosclerotic one, a series which might point to the pathogenesis of atheroma:

(1) the normal vein—no subendothelial layer

(2) the vein under increased venous pressure—formation of a fibroelasticomuscular subendothelial layer

(3) the connective tissue plaque—a focal and exaggerated replica of 2

(4) the fibrolipoid plaque—atheroma

As Cramer [18] said: "Sclerosis of vascular walls is seen in its purest and simplest form in the veins where degenerative changes remain minimal and where, owing to the scanty development of the lesions, we are most likely to gain an understanding of their origin."

INCIDENCE

Of the total number of 245 veins examined, 108, i. e., 44 per cent, showed sclerotic plaques. This is a slightly lower incidence than Schilling's, who found them in 50 per cent. Among the 147 males the incidence was 44.2 per cent, and among the 98 females it was 43.9 per cent. There is thus no sex difference. Neither was there in Schilling's series. The incidence in the various age groups is given in table 1. It can be seen that while there is a definite trend toward more frequent occurrence with advancing age, the correlation is by no means close. In an attempt to uncover etiologic associations the following groups were analyzed:

1. Fifty persons dying with an acute infection; of these, 22, i. e., 44 per cent, showed venous plaques (not corrected for age).

2. Fifty-nine persons furnishing presumptive evidence of a disturbance of cholesterol metabolism in the direction of hypercholesteremia, viz., persons suffering from one or more of the following conditions: gallstones, obesity, diabetes, myxedema, nephrosis or biochemically proved hypercholesteremia. Of these, 28, i. e., 47.4 per cent, showed venous plaques. This higher incidence is, however, entirely due to the age distribution, and an analysis according to age groups shows that the

incidence of venous plaques is, if anything, smaller in this group than in the total series (table 2).

3. Thirty-one persons who had evidence of increased intravenous pressure. Of these, 45 per cent showed venous plaques (not corrected for age).

TABLE 1.—*Incidence of Venous Atheroma According to Age Groups*

Age Group	Persons in Group	Number with Plaques	Percentage with Plaques	Schilling's Percentage
0-20	30	8	26.7	..
20-39	24	7	29.1	43.75
40-49	47	22	46.8	29
50-59	52	24	46.1	43
60-69	55	33	60	67
70-79	34	11	32.3	62
80-85	3	2	66	..

TABLE 2.—*Comparison of Rates of Incidence of Venous Atheroma in Age Groups of Whole Series and of Group with Cholesteremic Tendency*

Age Group	Percentage of Persons with Plaques	
	Whole Series	Group with Cholesteremic Tendency
41-45	38	14.5
46-50	59	80
51-55	50	40
56-60	40	50
61-65	64	64
66-70	54	50
71-75	30	43
76-80	40	40

TABLE 3.—*Incidence According to Degrees of Atheroma of the Aorta*

Degree of Atheroma Aortae	Persons in Group	Number with Venous Atheroma	Percentage with Venous Atheroma
Minimal	19	6	31.5
Mild	53	24	45.2
Moderate	44	19	43.1
Marked	35	17	48
Severe	7	2	28
Total	158	68	43

Thus none of these three groups seems to be significantly linked with the occurrence of venous plaques.

Finally 158 persons in whom the extent and the severity of aortic atheroma had already been determined were studied with regard to the incidence of venous atheroma. For this purpose each was assigned to one of five groups as having minimal, mild, moderate, marked or severe aortic atheroma. The result is summarized in table 3, which

shows that there is no correlation between the severity of aortic atheroma and the occurrence of the venous plaques.

Schilling, too, was unable to establish any etiologic link between the occurrence of venous atheroma and the extent or the severity of the atheromatous lesions of the aorta. In his analysis there was a fairly well marked correlation between venous congestion and venous atheroma, 33 of 75 persons with venous plaques having suffered from venous congestion as against 13 of 75 persons without plaques. I was unable to confirm this relation.

ETIOLOGIC CONSIDERATIONS

Venous atheroma, speaking in general, is a great rarity. What, then, are the circumstances which produce it with considerable frequency in one particular location of the venous system?

A glance at the topography of the area of bifurcation will reveal the fact that here is the place of maximal mechanical stress in the whole venous system. The right common iliac artery crosses in front of the orifice of the left common iliac vein in such a manner as to compress this vessel once every systole between itself and the vertebral column.[18] There is no cushioning to lessen this effect.

The most impressive and often the only venous atheroma is found just at the center of this area of rhythmic compression. In addition, owing to the large diameter of the veins concerned and owing to the fact that the inferior vena cava possesses no valves, venous pressure at this point is also at its maximum. The arterial pressure exerted on the veins from the outside is also greater here than at the similarly built confluences of internal and external iliac veins (although even at these lesser bifurcations slight venous sclerotic changes are not infrequently found). It is in this region that the elsewhere fairly mobile inferior vena cava is firmly fixed to the aorta by connective tissue. Finally, here is a place where the returning venous stream changes its direction as it leaves the pelvis for the abdomen.

It is impossible to find a place in the whole venous system at which the vascular parietes are subjected to a greater or more constant mechanical stress.

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18. The real nature of this compression can be gaged from the fact that in nearly every case the last half-inch of the left common iliac vein is widely dilated from the constant damming back of blood in it. Measurements taken in a great number of cases have shown that the proximal part of the left common iliac vein has a circumference on the average nearly twice that of the proximal part of the right common iliac vein. It forms a sort of venous sinus between the limbs of the arterial bifurcation. In the case of the left vena cava, however, the measurements were reversed, the circumference of the right common iliac vein being twice that of the left (3 vs. 1.5 inches).

The cholesterol content of venous blood is as great as that of arterial blood,[19] and if the instability of this substance were the essential cause of atheroma, one would expect atheroma to occur in many locations of the venous tree. A lesion as strictly localized as the one described in this paper must have a local cause and this I see in the mechanical stress to which the veins are subjected at this point. One case in which there was sinistroposition of the inferior vena cava and in which there was exhibited a mirror image distribution of the sclerotic lesion lends force to this opinion. It seems, therefore, that even if an instability of blood cholesterol were conceded as a necessary cause of atheroma that it can only exert its action in the presence of mechanical stress.

Schilling's conclusions about the causation of venous atheroma are similar. He said:

> . . . Phlebosclerosis can exhibit the same degenerative changes (hyalinization, fatty changes, calcification) in the same degree as arteriosclerosis, but always only in locations which through special anatomical and functional circumstances are subjected to strong mechanical stresses.

COMMENT

The finding of intimal thickenings containing intracellular and extracellular fat with splitting of elastica, hyalinization and calcification makes the identification of these lesions as atheroma secure. Whether the purely fibrous plaque occurring in the same location can also be regarded as atheroma is a matter of opinion. Fibrosis is a constant feature of arterial atheroma, and purely fibrous plaques do occur in arteries. If one insists on the demonstration of fat in every case before classifying it as atheroma the effect would be to reduce the incidence of venous atheroma from approximately 50 to approximately 25 per cent. The main argument would remain unaffected. Therefore one concludes that at least 25 per cent of all adults show venous atheroma. This atheroma is of a mild type and much more inclined to heal by fibrosis than its arterial counterpart.

The immunity of veins respecting atheroma argues that an essential atherogenetic factor is lacking in them. The fact that atheroma occurs at one particular spot of the venous tree with considerable frequency argues that this missing essential atherogenetic factor is present at that one spot in the venous system. The atheroma-bearing spot is found to differ from the rest of the venous system in being the point of maximal mechanical stress. This sums up to the following thesis:

(1) That the essential atherogenetic factor is the mechanical stress on the vascular wall,

19. Shillito, F. H.; Bidwell, E. H., and Turner, K. B.: J. Biol. Chem. **112**: 557, 1935.

(2) That the immunity of veins as regards atheroma is not due to a different composition of venous blood nor to a different reactivity of the venous wall but to the absence of mechanical stress comparable to that acting on the arteries,

(3) That where mechanical strain of comparable magnitude exists veins develop atheroma in much the same way as arteries do.

The analysis of these cases of venous atheroma thus furnishes a further argument in favor of the widely held opinion that mechanical stress is the fundamental etiologic factor of atheroma. It must be clearly understood that in putting forward this etiologic proposition no pronouncements whatever are made about the pathogenesis of atheroma. How pressure works its effect, whether by upsetting the stability of blood cholesterol, whether by traumatizing the endothelium, whether by simply massaging an excess of plasma into the intima, etc., is a different question altogether. But in trying to answer these pathogenetic questions investigators should never lose sight of the basic etiologic factor, viz., pressure. It is in the belief that the pathogenetic researchers, especially of the "cholesterol" school of thought, are tending to obscure this fact that I present this contribution.

If venous atheroma is determined by local factors, it is not surprising that neither Schilling nor I was able to demonstrate any correlation between the severity of aortic atheroma and the occurrence of venous atheroma. However, in most cases of calcified venous atheroma (6 out of 8) there was also severe calcification of the aortic lesions. This suggests that while atheroma is largely determined by local conditions, a systemic factor is concerned in the production of grossly calcified atheroma. This idea gains support from the fact that in this small group of cases one found evidence of either metastatic calcification or some other upset of calcium metabolism. I intend to deal fully with this aspect of calcified atheroma in a separate paper.

SUMMARY

In almost half of all adults atheromatous plaques are found in a small area comprising the proximal end of the left common iliac vein and the medial distal 2 cm. of the inferior vena cava. The fact that atheroma occurs at the point of maximal mechanical stress in the venous system should be taken into account in any reasoned assessment of the problem of atheroma.

UNUSUAL FORMS OF BLASTOMYCES DERMATITIDIS IN HUMAN TISSUES

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DURHAM, N. C.

GILCHRIST [1] published the first description of blastomycosis in 1896. Since then, many cases of Blastomyces dermatitidis infection have been described.[2] These reports have illustrated the usual tissue findings in the different types of human blastomycotic infections. In the course of study of a case coming to autopsy at Duke University Hospital in which pulmonary blastomycosis complicated carcinoma of the gallbladder, many unusual forms of the organism were found. Some of these were smaller than any previously described in tissues and were so similar to Histoplasma capsulatum that they might easily have been confused with that organism.

The patient was a 76 year old white woman in whom chills, fever and a palpable abdominal mass developed in September 1948. A week later, after induction of ether anesthesia, cholecystotomy was done, with removal of many gallstones. Following the operation, the patient had persistent bile-stained abdominal drainage and periodic night sweats. She continued to fail, losing about 50 pounds (22.5 Kg.) of weight, until late January 1949, at which time the bile drainage ceased and jaundice promptly developed, with severe abdominal pain, anorexia, nausea and vomiting.

As a child she had typhoid, and in 1942 and 1944 tumors were removed surgically and with irradiation from her left ear and from below her eye, which were diagnosed as epithelioma. A deep, pitted wound in the side of her head, draining foul pus, persisted for the remainder of her life.

On entry she was heavily jaundiced and emaciated. Her left ear was absent; in its place was the crater of an ulcer approximately 1.5 cm. in diameter and 1 cm. deep, in the base of which was necrotic bone. Aside from this and the healed surgical scar her skin showed no lesions. Her lungs were clear. Her heart was normal. Her abdomen revealed a smooth and somewhat tender mass in the right upper quadrant which moved with respiration and seemed to be attached to the liver. Roentgenograms of the chest revealed moderate calcification in both hilar regions and linear radiation from the hilus into both upper lobes, suggesting scarring and perhaps old fibroid tuberculosis.

The patient seemed to be failing so rapidly, despite routine therapy, including transfusions, that surgical relief was attempted. Under local procaine anesthesia, the old operative incision was opened. About 300 cc. of thick, green pus was

From the Department of Pathology, Duke University School of Medicine.

1. Gilchrist, T. C.: Johns Hopkins Hosp. Rep. **1**:269, 1896.

2. Martin, D. S.; and Smith, D. T.: Am. Rev. Tuberc. **39**:275, 1939.

drained, several small gallstones were removed, and a biopsy was made of an irregular, nodular mass in the gallbladder, which revealed a well differentiated carcinoma. After the operation her condition remained poor, and despite supportive therapy, penicillin, transfusions and oxygen she gradually sank into a deep coma, became cyanotic and died quietly on the fifth day after the operation.

At autopsy the chest was emphysematous. In the right upper abdominal quadrant was a relatively fresh surgical wound from which semipurulent, bile-stained fluid drained. There were fibrinous pleural adhesions in the right side of the chest and more dense fibrous adhesions laterally and posteriorly in the left side of the chest. There was no fluid in either thoracic cavity. The abdomen contained about 600 cc. of clear ascitic fluid. All of the organs were deeply jaundiced. A large mass was found in the region of the gallbladder, adherent to the skin and all neighboring viscera.

The right lung showed hemorrhagic, confluent lobular pneumonia in the lower lobe. The middle and upper lobes of the right lung and the entire left lung showed patchy irregular gray areas of variable size which felt much like pebbles embedded in the lung parenchyma. In addition to the large solid areas there were tiny granular foci resembling miliary tubercles scattered throughout. Little of the lung tissue looked normal, and crepitation was absent or minimal throughout. Hilar lymph nodes were scarred and calcified. The liver showed early cirrhosis and several small metastases, some of which had caused obstruction of the left main hepatic biliary duct. The gallbladder was incorporated into a dense fibrous and fatty mass adherent to the abdominal wall, the liver, the duodenum, the pancreas and the body wall. It showed a central empyema cavity with a necrotic inflammatory lining and an irregular annular lesion, diagnosed as carcinoma.

Postmortem cultures of material taken from various sites showed beta hemolytic streptococcus, Escherichia coli and Klebsiella pneumoniae. The cultures for fungus were unfortunately discarded when these organisms were identified.

Microscopic examination showed that the gallbladder was the seat of an adenocarcinoma which had metastasized to the liver, the head and tail of the pancreas, the left adrenal gland and to many abdominal lymph nodes. A single focus of microscopic size was found in the left lung.

The other abnormalities found in the lung proved to be granulomatous in nature. There were solid tubercle-like lesions with fibrosis and definite epithelioid cell and giant cell formation. There was, in addition, granulomatous pneumonia with extensive fibrosis, lymphocytic and polymorphonuclear exudate and, again, many giant cells. In many of the giant cells organisms were found varying from tiny granules, each surrounded by a vacuole, to very large solid forms, each showing a hyaline capsule. No endosporulation was noted, and budding forms were common. In no case were there multiple buds on a single organism. All transitions were found between the various forms noted, and in the fresh wet preparations the tiny forms also showed hyaline capsules.

The lesions removed from the left ear in 1942 and 1944 were reviewed, and they showed basal cell carcinoma. In addition, a granulomatous focus was found at one point, but no organisms could be identified in this tissue.

COMMENT

The relationship of carcinoma of the gallbladder and cholelithiasis has been well described; this case adds nothing to the literature on that account.

The lesions of the lungs show organisms of remarkably variable form. Large areas within a lesion show a tiny form of the organism and an inflammatory reaction made up of large mononuclear macrophages (fig. 1), although the tiny form is found also in giant cells. The organisms resemble H. capsulatum, save that they are slightly larger, and the inflammatory reaction resembles that of histoplasmosis in many respects. The smallest forms of the organism appear to show the greatest shrinkage in preparation of histologic slides, and as a consequence more closely approximate the size of H. capsulatum. Forms measuring from 2.2 to 16.5 microns were found in the tissues. The organisms found in wet preparations made by scraping the cut surface of the lung and mounting in saline solution measured from 4.4 to 16.5 microns.

The cultural proof that these are B. dermatitidis is lacking. However, the characteristics of the organism are so clearcut that there is little room for question. The presence of budding forms, the absence of forms showing multiple buds, the relative thinness of the capsule in india ink preparations, the absence of endosporulation, the absence of mycelial growth in tissues and finally the size of the larger forms of the organism are all in accord with this diagnosis. In addition, the morphologic aspects of the smaller forms are identical with those of the others save for the size. The budding of the smallest forms is like that of Blastomyces and is not the constrictive type of the yeasts. The fact that all intermediate forms can be traced between the smallest and the largest organisms (fig. 2) and that the smallest forms morphologically resemble B. dermatitidis is assurance that this is not a mixed infection. Furthermore, the larger organisms are identical with the common form of B. dermatitidis (fig. 3), and the inflammatory reaction is a tubercle and giant cell–forming one like blastomycosis for the most part.

Small forms have been observed in cultures of this organism.[3] Wade[4] observed equally small organisms in a lesion of the skin, but the described characteristics differed markedly from the ones observed in this case.

The site of origin of the infection seems most likely to have been pulmonary. It is interesting to note with regard to systemic blastomycosis that the lungs are involved in over 90 per cent of the cases and are the chief organ involved in over 50 per cent of the cases. No relation could be found between the carcinoma and the blastomycosis save for the one tiny area in the lung where they coexisted.

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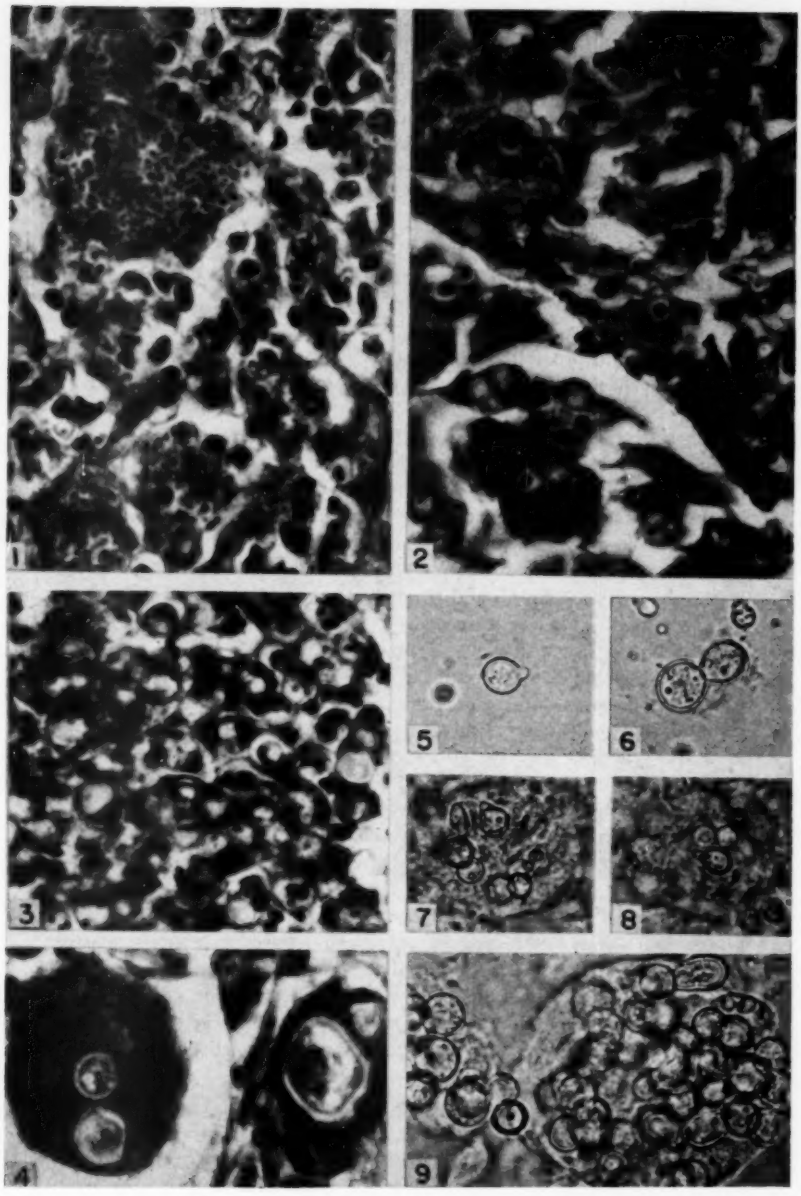
3. Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. L.: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1944.

4. Wade, H. W.: J. Infect. Dis. **18**:618, 1916.



Figures 1-9

(See legend on opposite page)

It is interesting to speculate on the possibility that there was a relationship between the debilitation produced by the carcinoma of the gallbladder, the jaundice and the patient's age, and the unusual picture of pulmonary blastomycosis found in this case. Further, it is considered possible that the ether anesthesia used in the first operation, five months before death, might have played a part in the development of the fulminating involvement seen in the lungs. However, the factor of virulence of the organism cannot be evaluated in this case.

SUMMARY

Forms of Blastomyces dermatitidis smaller than those previously recorded are described as observed in tissues.

The possibility that blastomycosis and histoplasmosis may be confused because of these small forms is emphasized.

EXPLANATION OF FIGURES 1-9

Fig. 1.—Small forms of Blastomyces dermatitidis in lung; hematoxylin and eosin; × 720.

Fig. 2.—Transition between the small and the usual forms of B. dermatitidis in lung; hematoxylin and eosin; × 720.

Fig. 3.—Forms of B. dermatitidis of the usually described type in lung; hematoxylin and eosin; × 720.

Fig. 4.—B. dermatitidis within giant cells in lung; hematoxylin and eosin; × 720.

Figs. 5 and 6.—Budding forms of organism; wet preparation from lung; × 720.

Figs. 7 and 8.—Small forms of organism showing budding; wet preparation from lung; × 720.

Fig. 9.—Usually described type of organism within a giant cell; wet preparation from lung; × 720.

URTICARIA PIGMENTOSA

A Report of a Case with Autopsy

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URTICARIA pigmentosa has been recognized as a clinical entity since Nettleship [1] described it in 1869. Unna [2] elaborated the histopathology of the lesions of the skin in 1887 by showing that there were dense accumulations of mast cells or tissue basophils in both the macular and the papular type. This was subsequent to the work of Erlich,[3] who had differentiated mast cells from the other connective tissue elements by the use of a toluidine blue stain which brings out the blue cytoplasmic granules. Small numbers of these cells are scattered through normal tissue in man and other animals, and it is believed their relation to the blood basophilic cells is probably only morphologic. Maximow, Downey and Ringoen [4] concluded that the mast cells originate in connective tissue while the blood basophils are derived from the bone marrow. The nucleus of the mast cell is single and round or oval, while that of the blood basophil is like that of the polymorphonuclear leukocyte.

Recent interest in the role of the mast cell has been stimulated by Holmgren and Wilander [5] and Jorpes, Holmgren and Wilander,[6] who have concluded that the mast cell is the elaborator of heparin. Bloom [7] described mast cell tumors in dogs, and Oliver, Bloom and Mangieri [8] assayed these tumors, finding their heparin content "50 times that of

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1. Nettleship: Brit. M. J. **2**:323, 1869.

2. Unna, P. G.: The Histopathology of the Skin, translated by N. Walker, Edinburgh, New York, The Macmillan & Co., 1896, p. 955.

3. Erlich, P.: Arch. f. Anat. u. Physiol. **3**:166, 1879; **4**:571, 1879.

4. Maximow, A.: Arch. f. micr. Anat. **67**:680, 1906; **83**:247, 1913. Downey, H.: Folia haemat. **16**:49, 1931. Ringoen, A. R.: Am. J. Anat. **31**:319, 1923.

5. Holmgren, H. J., and Wilander, O.: Ztschr. f. mikr.-anat. Forsch. **42**:242, 1937.

6. Jorpes, J. E.; Holmgren, H. J., and Wilander, O.: Ztschr. f. mikr.-anat. Forsch. **42**:279, 1937.

7. Bloom, F.: Arch. Path. **33**:661, 1942.

8. Oliver, J.; Bloom, F., and Mangieri, C.: J. Exper. Med. **86**:107, 1947.

dog liver." Lately there have been reports of large numbers of mast cells in the victims of the atomic bomb dying approximately one month after exposure.[9] There was a widespread hemorrhagic state in these victims [10] and also in the test animals at Bikini,[11] whose blood when titrated with antiheparin substances seemed to indicate that an anticoagulant was present.[12] This was partial confirmation of the work of Allen and Jacobson,[13] who exposed dogs to total body ionizing irradiation. They expressed the belief that their experimental evidence shows that the substance causing the hemorrhages is heparin.

A classic study of urticaria pigmentosa was presented by Little,[14] who reviewed all the cases (154) reported up to 1905. In 1923 Finnerud [15] reviewed 152 additional cases, and since that time from one to five reports have been published each year, usually describing some unusual feature of the disease. However, there has never been report of an autopsy as far as can be determined by a search of the available English, German and French literature. The absence of such a report might be considered extraordinary in view of the relative frequency of urticaria pigmentosa except for the fact that the disease has been thought nonfatal. Ormsby [16] stated that "the active reproduction of the lesions commonly subsides spontaneously after a certain number of years." This is substantially the opinion of all authors of standard textbooks of dermatology.

The purpose of this paper is to present the case of a Negro girl born with macular and papular lesions later demonstrated to be histologically identical with those of urticaria pigmentosa. The child died at the age of 12 months and 19 days. The clinical history, the gross autopsy findings and a comparative histologic study are presented in that order.

REPORT OF CASE

C. M. C. was born in this hospital, July 5, 1946, after nine months of pregnancy. Seven months prior to the birth the mother was found to have a purulent discharge of the cervix. Smear and culture showed gonococci. Syphilis was ruled out clinically, and the serologic tests were negative prior to and after the administration of 200,000 units of penicillin, which resolved the gonorrhea.

The infant's birth weight was 2,800 Gm. Her respiration was spontaneous. Her lusty cry and physical condition were declared good. Beneath the vernix caseosa were elevated nummular grayish nodular lesions on forehead, thighs and

9. Liebow, A. A., and Warren, S.: Am. J. Path. **23**:888, 1947
10. LeRoy, G. T.: J. A. M. A. **134**:1143, 1947.
11. Tullis, J. L.: Am. J. Path. **23**:891, 1947.
12. Cronkhite, E. P.: Am. J. Path. **23**:891, 1947.
13. Allen, J. G., and Jacobson, L. O.: Science **105**:388, 1947.
14. Little, G.: Brit. J. Dermat. **17**:355, 1905; **18**:16, 1906.
15. Finnerud, C. W.: Arch. Dermat. & Syph. **8**:344, 1923.
16. Ormsby, O. S.: A Practical Treatise on Diseases of the Skin, Philadelphia. Lea & Febiger, 1937, p. 153.

back, measuring 0.5 to 1 cm. (fig. 1). Some had a semitranslucent appearance, but all were firm, solid lesions. In addition, there was a diffuse reddish purple elevated rash on the face and the thorax.

A specimen of skin was taken for biopsy on August 7. The patient was sent home on August 9 with a note, "she is clinically well and gaining weight."

The routine hematoxylin and eosin stain of the skin taken for biopsy showed numerous inflammatory cells of the monocytic series in the corium. No specific diagnosis was made. The biopsy slides were submitted by Dr. H. V. Allington at

Fig. 1.—Lesions of the skin at birth.

a dermatologic meeting, where it was suggested that the possibility of urticaria pigmentosa be considered.

The biopsy material was then stained with Giemsa stain and azure II, which revealed that a large portion of the cells infiltrating the corium were mast cells. The patient was readmitted to the hospital, April 10, 1947, with a chief complaint of swelling of the abdomen for the preceding two months and the skin rash which had been present since birth. The mother had given the child ½ teaspoon of castoria® daily for five months but did not explain why. The baby had had three soft, yellow-green bowel movements each day and had scratched herself

for the preceding three months, but the rash was described as lessened in amount since the previous admission.

The family history revealed that there was one other child, aged 3. That child, the father and the mother were all living and well. There was no known tuberculous exposure.

Examination showed many pigmented spots over the body. The anterior fontanel was open and large. The ear drums and canals were clear. No rigidity or masses were noted in the neck. The pupils were round and regular and reacted to light and distance. The chest was normal to percussion; no adventitious sound

Fig. 2.—The mast cell infiltration of the corium.

was heard. The heart rhythm was regular; the rate, 110; no murmurs were heard. The abdomen was swollen, tense and tympanitic. The liver extended 4 cm. below the right costal margin. The spleen was questionably palpable. Hyperactive peristalsis was noted. The extremities were wasted, with no paralysis, deformities or edema; the reflexes were normal.

The stools were voluminous and foul smelling. The baby was restricted to a low fat, low residue banana diet but ate poorly, and in a few days diarrhea developed. She was treated with penicillin, 10,000 units intramuscularly every three hours, until the diarrhea cleared up, as it did after a short period. Her

temperature varied between 98 and 100.2 F. without a characteristic curve. On June 21 liver was taken for biopsy and the hematoxylin, eosin stain showed early portal cirrhosis. There was no evidence of lipid infiltration. Previously, on May 22, a marrow smear showed active hemopoiesis with no evidence of infiltrating abnormal cells. On July 24 the patient died.

Roentgen examination (barium sulfate enema) showed marked looping of the descending colon. The lumen was dilated, but not extremely. Roentgenograms of the skull were negative for Hand-Christian-Schüller disease.

The Kline test was negative. The hemoglobin content on admission was 8.6 Gm.; the count of white blood cells was 16,700, with 45 segmented cells, 8 band cells, 5 metamyelocytes, 40 lymphocytes and 2 monocytes per hundred. The urine was alkaline, with a faint trace of albumin; there was no sugar. The icteric index was 2. A red cell fragility test showed hemolysis starting at 0.46 and complete at 0.28 per cent sodium chloride. Blood cholesterol was 88 mg. per hundred cubic centimeters. Titration of the gastric contents showed free hydrochloric acid 0 and total hydrochloric acid 6. Duodenal drainage showed amylase totaling 256 Somogyi units. A dextrose tolerance test showed: fasting blood sugar, 80 mg.; one hour, 116 mg.; two hours, 136 mg. Multiple stool specimens revealed no fat droplets. Cultures of the stools showed no pathogenic organisms and were repeatedly negative for ova and parasites. Five days before death the hemoglobin was 11.6 Gm., and the blood counts were 4,030,000 red cells and 12,100 white cells, with 21 segmented cells, 4 band cells, 3 metamyelocytes and 72 lymphocytes per hundred. Anisocytosis and achromia were noted.

Autopsy.—The body was that of a well developed, emaciated Negro girl 60 cm. in height and 5,200 Gm. in weight. A moderate amount of mucopurulent fluid was noted about the nares. No peripheral lymphadenopathy was found. The right lung weighed 50 Gm.; the left, 40 Gm. The pleural cavities were dry and the lungs free. The lower lobes and the dependent parts of the upper lobes were purplish and discolored, and had depressed areas in a patchy distribution on the pleural surface and on cut section. A small amount of frothy fluid could be expressed from the surface. The lungs were subcrepitant. The heart weighed 20 Gm. The pericardial sac contained about 5 cc. of a clear serous fluid. The pericardium was smooth and glistening and the myocardium moderately firm. The valves and the coronary arteries were normal. The thymus was small, atrophic, and there was a large number of greatly enlarged mesenteric and retroperitoneal lymph nodes of fairly uniform size, up to 1 cm. in diameter. These were soft and discrete and cut with ease, showing a uniformly pale, smooth surface. The liver weighed 320 Gm. Glisson's capsule was glistening, and the surface had an ill defined, mottled appearance with slightly rounded edges. On cut section, many stellate, grayish white areas were noted in portal spaces. The gallbladder was normal. The spleen weighed 55 Gm., was firm and adhered to the diaphragm by delicate fibrous adhesions. The capsule was slightly thickened and gray, with the cut section showing gray-white stellate areas in the pale parenchyma. The pancreas and the adrenal glands were grossly normal. The gastrointestinal tract showed no lesions. The right kidney weighed 40 Gm. and the left, 40 Gm. Both kidneys were deformed, the upper poles being depressed by the liver, the encroachment of which formed flat surfaces directed cranially and medially. The capsules stripped with ease. Their surfaces and cut sections were normal, as were those of the ureters and the bladder. The brain weighed 700 Gm. and showed no abnormalities.

Mast Cell Counts.—Tissues from various organs were fixed in a 4 per cent formaldehyde solution and stained with hematoxylin and eosin. Comparable sections were made from the tissues of normal infants of the same age because of the gradual decrease of normal mast cell counts with increasing age. All tissues were then stained with Giemsa stain after the method of Parsons and Black,[17] and comparative counts were made of the numbers of mast cells in the tissues of the patient as well as in those of the controls (see table). The counts tabulated represent the average number of mast cells per oil immersion field seen in the tissues of the patient as compared with the control counts. Mast cell counts were made in 10 cases of portal cirrhosis and 10 cases of Hodgkin's disease, and in no case was an increase found.

Description of Mast Cells Observed.—Two kinds of mast cells were seen. One had deeply stained metachromatic granules closely packed within the cytoplasm. The second had fewer, more widely spaced granules, which appeared to take up less dye, as though they had not reached or had gone beyond their maturity.

In some areas of the liver, where the mast cells were most numerous, it was possible to identify the basophilic cytoplasmic granules in the stroma beyond the cell walls. Cells having the same morphologic aspect as mast cells were seen in the sinusoids of the lymph nodes, spleen and liver and, in small numbers, in various other vascular channels in other tissues. The mast cells varied from 10 to 25 microns. Some were spherical, while others were stellate or lancet shaped. The nuclei were usually ovoid, but those of the stellate or lancet form were highly irregular. No morphologic difference could be noted between those of the patjent and those of the controls.

Weigert's method of staining the tissue did not reveal the inclusion bodies described by Bloom [7] in his canine cases of mast cell tumor.

Microscopic Description of the Tissues.—The liver showed extreme widening of the portal areas by connective tissue, which varied from adult collagenous to fibroblastic type. There was striking hyperplasia of the small bile ducts. In the areas of fibroblastic proliferation there were lymphocytes, plasmacytes, an occasional macrophage and eosinophilic granulocyte as well as large numbers of tissue mast cells. There were from 25 to 30 of these mast cells in each oil immersion field of the areas of fibrosis and from none to 2 mast cells in the undamaged portions of the parenchyma. Usually one border of the mast cell was in apposition to a sinusoid, but occasionally the cell was completely surrounded by parenchymal cells. An occasional mast cell was seen within the lumen of a sinusoid.

The periportal fibrosis seen in the biopsy specimen was not as marked as that present at the time of death. There was less hyperplasia of bile ducts and fewer, more immature mast cells in the fibrotic areas than at autopsy.

In the lung, marked intra-alveolar hemorrhage was found. Colonies of bacteria were observed in the bronchi and in the alveoli. There was patchy bronchopneumonia.

Two to 5 mast cells were seen in each oil immersion field of the pleura and the septal connective tissue. One to 3 mast cells could be seen in each oil immersion field of the parenchyma, chiefly in the alveolar wall and occasionally in an alveolus.

The splenic capsule and the trabeculae were very thick. The white pulp was diminished, and the germinal centers of the splenic corpuscles were not visible. The red pulp was moderately hyperemic, with large numbers of eosinophilic cells scattered throughout. There were 10 to 25 mast cells in each oil immersion field

17. Parsons, R. J., and Black, M.: To be published.

of the red pulp, but none was seen in the white pulp or in the capsule or the trabeculae. There were many areas in which fibrosis had taken place. Fibroblastic tissue was seen in the vicinity of older fibrosis.

The bone marrow immediately beneath the endosteum contained large numbers of mast cells and eosinophilic cells. There were 50 to 60 mast cells per oil immersion field in the marrow adjacent to the endosteum, with approximately 1 mast cell to each of all other types of marrow cells. The ratio of mast cells to other types of cells fell as one examined deeper into the marrow and away from the endosteum.

In the biopsy of marrow no mast cell or other abnormalities were seen.

The kidney revealed acute passive congestion, with many small hemorrhages of the medulla between the collecting tubules. From 2 to 5 mast cells were seen in each oil immersion field in the interstitial connective tissue surrounding the convoluted tubules and the loops of Henle in the cortex. No mast cells were seen in the medulla. From none to 3 mast cells per oil immersion field were

Mast Cell Counts (Average Numbers per Oil Immersion Field)

	Tissues of Normal Controls		Tissues of Patient	
Tissue	Parenchyma	Capsule or Surrounding Connective Tissue	Parenchyma	Capsule or Surrounding Connective Tissue
Liver	0-1	...	25-30	...
Lung	1-2	...	2-5	...
Spleen	0	...	10-25	...
Thymus	...	...	50-60	...
Bone marrow	0	...	50-60	...
Kidney	0-1	...	2-5	...
Pancreas	1-2	...	30-40	...
Urinary bladder	0-3	...	0-2	...
Ovary	0	0-1	0	0-4
Adrenal gland	0	0	0	3-5
Pituitary gland (anterior lobe only)	0	0-1	0	3-9
Cerebrum	0	...	0	...
Cerebellum	0	...	0	...
Lymph node 1	0	0-1	20-30	10-15
Lymph node 2	0	...	20-30	10-15
Lymph node 3	0	...	10-15	10-15

seen in the intercapillary spaces of the glomerular tuft, but these were not numerous.

In the pancreas there was extreme interstitial fibrosis with a relatively small amount of acinous tissue, which appeared to be undergoing atrophic changes. The connective tissue in many places was heavily infiltrated with lymphocytes, plasmacytes, histiocytes and mast cells. In many of the areas of interstitial fibrosis there were as many as 40 mast cells per oil immersion field, and in a few there were as many as 5 to 10 eosinophilic cells.

Acute passive congestion was noted in the urinary bladder. Only a very occasional mast cell was seen in the submucosa and the interstitial fibrous connective tissue of the muscle layers.

The ovary presented a normal histologic picture throughout. There were 1 to 4 mast cells per oil immersion field in the connective tissue of the hilus. No mast cell was seen in the parenchyma.

The adrenal gland had normal parenchyma except for slight hyperemia. There were several small hemorrhagic areas surrounding the adrenal gland, in the fat. Also, there were several islands of persisting fetal fat around the gland. No mast cells were seen in either the medulla or the cortex. There was from none

to 1 mast cell per oil immersion field in the capsule and from 3 to 5 mast cells in the fetal fat.

In the pituitary gland (anterior lobe only) there were several small hemorrhages in the capsule and in the parenchyma. The parenchyma was moderately hyperemic, but otherwise the structure was well preserved. There were 3 to 9 mast cells per oil immersion field in the true capsule and in the surrounding connective tissue. No mast cells were seen in the parenchyma.

Mast cells were not seen in the meninges or within the brain substance.

The capsule of a mesenteric lymph node (lymph node 1 in table) was thickened and the node enlarged. The germinal centers were present in normal numbers but were small, and the lymphoid cells were few. Very few mast cells were found in the germinal centers. The lymphoid cells in the reticulum were largely replaced by eosinophilic and mast cells, with 20 to 30 of the latter in each oil immersion field. The small blood vessels were widely dilated. Mast cells were scattered throughout the capsule and the trabeculae in about one-half the number found in the reticular areas. An occasional mast cell typical of those seen in the tissue was found in the lumen of a peripheral sinus.

Lymph node 2 was essentially the same as that described in the foregoing paragraph, in the general histologic aspect and in mast cell content.

Lymph node 3 also showed the same general histologic picture with about one-half the number of mast cells in the parenchyma and approximately the same number of mast cells in the capsule and the trabeculae.

The table shows comparative counts of the mast cells observed in various organs and tabulated as average numbers per oil immersion field. The controls were infants of the same age dying of traumatic lesions. There is an absolute increase in the number of mast cells in each organ in this case of urticaria pigmentosa as compared with the controls. This demonstrates urticaria pigmentosa as a systemic as well as a cutaneous disease.

COMMENT

The ultimate cause of death appears to have been pulmonary edema with aspiration of stomach contents, followed by early bronchitis. These features seem to be the sequelae of extreme cachexia.

As regards the underlying pathologic process leading to death, several possibilities were considered and ruled out clinically by laboratory examination or roentgenography. Hodgkin's disease was considered carefully, and there were histologic evidences of it, i. e., increased numbers of eosinophils and some fibrosis. No Reed-Sternberg cells could be demonstrated. However, Jadassohn [18] has taken simultaneous specimens for biopsy from patients with urticaria pigmentosa—one from a nonirritated lesion and one from a lesion irritated by scratching. The latter showed mast cells intermixed with large numbers of eosinophils. In the former eosinophils were absent. Mast cells were not present in significant numbers in any of the 10 cases of proved Hodgkin's disease in which tissues were examined in the course of this study.

Histologically, the liver shows portal cirrhosis, but cirrhosis is a rare disease in infancy, and too there were huge numbers of mast cells

18. Jadassohn, W.: Arch. f. Dermat. u. Syph. **167**:704, 1933.

in the liver of this infant which were not present in 10 cases of portal cirrhosis surveyed in this study. Sutton [19] searched the American literature in 1930 and found 12 cases of cirrhosis in childhood without a history of alcoholism and 10 cases with such a history. It is not possible to say more of the cirrhosis except to call attention to the parallelism in this patient and in Bloom's [7] dogs with mast cell tumors. Their skin lesions were similar. There were mast cells in the lung, bone marrow and periadrenal tissue and, most strikingly, the dog's livers exhibited "parenchymatous degeneration with periportal fibrosis and solitary and nodular collections of mast cells." The liver at biopsy as compared with the liver at autopsy contained fewer mast cells and less fibrosis and the nuclei of the mast cells were generally more vesicular, with the cytoplasmic granules more scattered and smaller. Paff, Bloom and Reilly,[20] who had followed mast cells developing in tissue cultures, stated that these less granular forms are immature.

Study of the autopsy material showed many points of similarity to cancer. There were multiple cutaneous tumors showing dense collections of mast cells with a certain pleomorphism as described. These cells were found in huge numbers in mesenteric lymph nodes, spleen, liver and bone marrow. There was a one to three fold increase over the number of mast cells seen in connective tissues of the controls. Mast cells were found quite frequently in the peripheral sinuses of the spleen. If the mast cells do, indeed, have extramyeloid origin as contrasted with the blood basophils, then the mast cells focally concentrated in the marrow of this patient must have been carried there by a metastatic process.

Touraine, Solente and Renault [21] have classified urticaria pigmentosa as a pseudoleukemia, citing the splenomegaly and lymphoid hyperplasia as evidence. They did not present evidence from biopsy of the spleen or the lymph nodes but stated that these are often clinically enlarged. It may be noted here in passing that Fabris [22] and Schreus [23] have produced mast cell tumors in mice by applying tar to the skin. This is consistent with the tar induction of certain other neoplastic diseases.

The significance of this study appears to be that it demonstrates urticaria pigmentosa as a systemic and not a purely dermal disease as it has been considered by many. The disease might be compared with lupus erythematosus in this regard. If this case can be considered one

19. Sutton, T. L.: Am. J. Dis. Child. **39**:141, 1930.

20. Paff, G. H.; Bloom, F., and Reilly, C.: J. Exper. Med. **86**:117, 1947.

21. Touraine, Solente and Renault, P.: Bull. Soc. franç. de dermat. et syph. **40**:1691, 1933.

22. Fabris, A.: Pathologica **19**:157, 1927.

23. Schreus, H. T.: Dermat. Ztschr. **40**:9, 1924.

of a true cancer in the classic sense, then it appears to be the first reported human case and may be compared with the canine cases of Bloom.[7]

Another interpretation must be considered, namely, an alteration of physiology. If it could be assumed that the mast cell is the originator of heparin, it would be reasonable to assume that there was some mechanism calling for an increased production of heparin. This was present in utero inasmuch as the tumors were present at birth. The gonococcic infection that was found in the cervix during the second month of pregnancy appears to have been the only untoward incident in the puerperium. Coincidentally, mast cells may be found in greatly increased numbers surrounding areas of chronic inflammation such as infected pilonidal cysts and fistula in ano.

Résumé of Comment.—What appears to be the first report of an autopsy made in a case of urticaria pigmentosa has been presented. Some light has been shed on the systemic occurrence of the disease, which heretofore has been lacking. The cause is not established by this study, nor is the relation of the disease described to classic urticaria pigmentosa absolutely clear. In cases of the latter the patient usually survives to die of some other disease after the urticaria has regressed. This patient's disease may be an example of cancerous mastocytoma similar to the mast cell tumors described by Bloom in dogs, and may confirm the hypothesis of Touraine, Solente and Renault that urticaria pigmentosa is a pseudoleukemia, or it could represent the histologic response to an alteration of psysiology, pointing to the gonococcic cervicitis that was discovered during the second month of pregnancy.

SUMMARY

A study is presented of an infant dying in the active phase of urticaria pigmentosa. This appears to be the first instance in which a study of the internal lesions of this disease has been made.

Increased numbers of mast cells were found in many portions of the body, with special attention being drawn to the lymph nodes and bone marrow, where the collections of cells simulate metastatic lesions. The liver showed a process of cirrhotic fibrosis bearing a similarity to the processes described by Bloom in canine cases of mast cell tumor.

The lesions of the skin were congenital, and the mother had gonococcic cervicitis in the first trimester of carrying this infant. Numerous mast cells are to be seen in the vicinity of many chronic infections. These facts may be related, and it can be postulated that this infant's congenital lesions might be the result of a localized demand for heparin due to the adjacent cervicitis.

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VIRUS-LIKE GLOBULES IN CANCER EXTRACTS

Electron-Microscopic Studies of Thirty Human Tumors

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IN A REVIEW of the literature concerning the properties of cancer cells Cowdry [1] in 1940 concluded that there was no reliable basis on which to reach a decision as to whether a single cell observed in a section of suspected tissue is or is not "malignant," and he stated that there is no satisfactory evidence that "malignant cells" of man possess anything—virus or otherwise—which is wholly absent in normal cells. Both statements seem to be refuted by recent studies made with the electron microscope.

In 1947 Claude, Porter and Pickels [2] observed in the cytoplasm of chicken tumor cells small spherical bodies ranging in diameter from 67 to 80 millimicrons. These were interpreted as the transmitting agent of chicken sarcoma. At the same time, Porter and Thompson [3] published electron micrographs of rat sarcoma cells which showed similar dense granules with a diameter of from 50 to 250 millimicrons. While the authors hesitated in suspecting that specific virus particles were seen in these globules, they regarded them as morphologic characteristics of "malignant cells."

In 1948 Porter and Thompson [4] observed spherical bodies which had an average diameter of 130 millimicrons in cultured mouse carcinoma cells. The uniform morphologic aspect and association of these bodies in closely packed clumps suggested to them that the bodies were of extraneous origin and probably represented the virus-like milk factor. In size the particles observed by Porter and co-workers differed greatly from the globules described by English investigators. Passey, Dmochowski, Astbury and Reed [5] treated tissue extracts with

This investigation was aided by a grant from the American Cancer Society (Kansas Division).

From the Electron Microscope Laboratory of the Sedgwick County Tumor Clinic and St. Francis Hospital.

1. Cowdry, E. V.: Arch. Path. **30**:1245, 1940.
2. Claude, A.; Porter, K. P., and Pickels, E. G.: Cancer Research **7**:421, 1947.
3. Porter, K. R., and Thompson, H. P.: Cancer Research **7**:431, 1947.
4. Porter, K. R., and Thompson, H. P.: J. Exper. Med. **88**:15, 1948.
5. Passey, R. D.; Dmochowski, L.; Astbury, W. T., and Reed, R.: Nature, London **160**:565, 1947.

benzin and trypsin and filtered them through a Berkefeld filter. They found in such extracts of tumors of mice of high breast cancer strains spherical particles with a diameter of only 20 millimicrons.

Using a high speed microtome which allows the cutting of tissue sections 0.1 micron thick, Gessler and Grey [6] demonstrated in human cancer tissue spherical bodies ranging from 80 to 150 millimicrons. Since there was a close similarity between these globules and the virus of fowl sarcoma, they supposed that they were probably dealing with virus-like causative agents of cancer cells.

Summary of Electron-Microscopic Observations

Patient	Age	Sex	Histologic Diagnosis	Method of Preparation	Size of Globules, Millimicrons
1	30	F	Melanoma	Maceration in water	20-95
2	54	F	Melanoma	Pepsin digestion	35-60
3	66	M	Carcinoma of bladder	Pepsin and trypsin digestion	Absent
4	22	F	Melanoma	Pepsin digestion	Absent
5	40	F	Medullary carcinoma of breast	Trypsin digestion	75-95
6	55	F	Metastatic carcinoma of ovary	Trypsin digestion	80-108
7	49	F	Duct cell carcinoma of breast	Trypsin digestion	30-105
8	39	F	Squamous cell carcinoma of vulva	Trypsin digestion	53-160
9	50	F	Duct cell carcinoma of breast	Benzin-water extract	60-108
10	68	F	Metastatic adenocarcinoma in lymph node	Saline extract	53-120
11	64	F	Duct cell carcinoma of breast	Benzin-saline extract	55-160
12	59	M	Hodgkin's disease	Benzin-saline extract	27-60
13	56	F	Metastatic melanoma in lung	Benzin-saline extract	80-120
14	48	F	Duct cell carcinoma of breast	Benzin-saline extract	85-175
15	49	M	Hodgkin's disease	Maceration in water	33-67
16	62	F	Squamous cell carcinoma of cervix	Water extract	40-80
17	66	F	Squamous cell carcinoma of cervix	Pepsin digestion	27-54
18	65	F	Anaplastic carcinoma of bladder	Pepsin digestion	33-67
19	30	F	Melanoma	Pepsin digestion	53-93
20	67	M	Papillary carcinoma of rectum	Acetic acid	53-160
21	68	M	Papillary carcinoma of bladder	Water extrast	27-40
22	36	M	Melanoma	Water extract	56-95
23	56	F	Adenosarcoma of uterus	Water extract	28-88
24	35	F	Chronic cystic mastitis	Benzin-saline extract	40-80
25	38	F	Fibroadenoma of breast	Benzin-saline extract	60-95
26	18	F	Fibroadenoma of breast	Benzin-saline extract	33-73
27	23	F	Fibroadenoma of breast	Benzin-saline extract	27-60
28	42	F	Meningioma	Benzin-saline extract	40-55
29	46	F	Fibroadenoma of breast	50% acetic acid	53-80
30	64	F	Lymphadenoid goiter	Saline extract	25-60

The importance of these electron-microscopic observations cannot be overemphasized. Should it be possible to see these particles in cancers of human origin in routine examination, the hundred year old problem of the "single cell" diagnosis of cancer (Hellwig,[7] 1932) would be solved.

MATERIALS AND METHODS

Twenty-three cancerous and 7 benign tumors of human origin have been studied during the last two years in the laboratory of the Sedgwick County Tumor Clinic and St. Francis Hospital with the electron microscope. Different methods of preparing tissue extract were tried; for instance, maceration in water, crushing

6. Gessler, A. E., and Grey, C. E.: Exper. Med. & Surg. **4**:307, 1947. Gessler, A. E.; Grey, C. E., and McCarty, K.: ibid. **6**:329, 1948.

7. Hellwig, C. A.: Arch. Path. **13**:607, 1932.

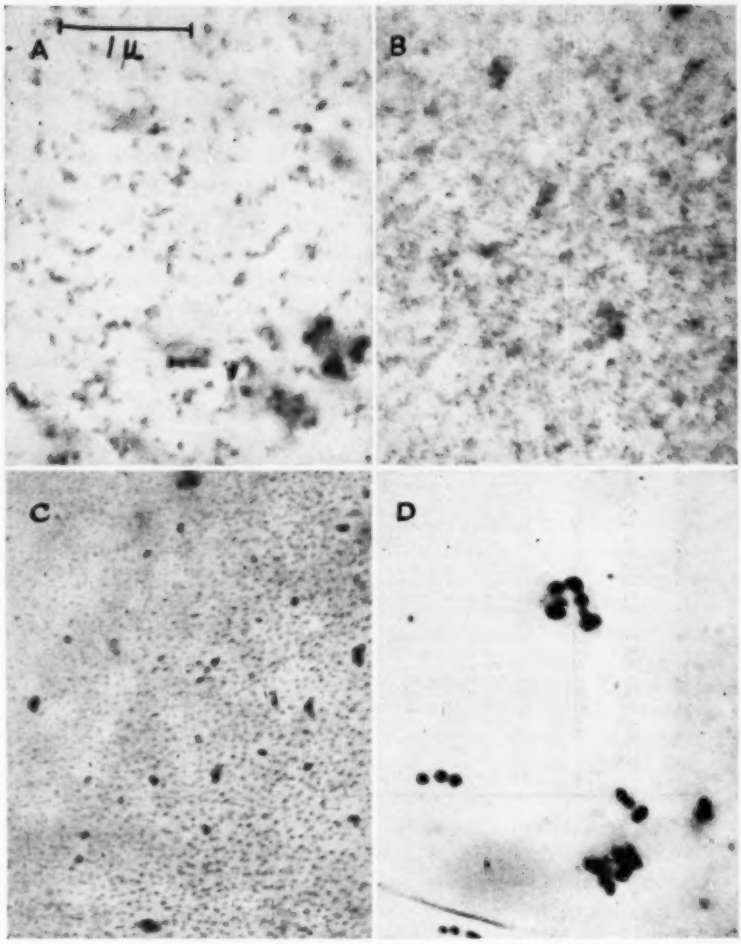

Fig. 1.—*A*, lymphadenoid goiter (case 30); small spherical globules forming chains and clusters. *B*, meningioma (case 28); small spherical particles measuring between 40 and 50 millimicrons. *C*, Hodgkin's disease (case 15); small globules and some aggregates of larger micelles. *D*, carcinoma of breast (case 11); large globules in pairs and short chains.

These electron micrographs were taken at a magnification of 5,000 diameters and photographically enlarged 4 times, so that final magnification is 20,000.

of tissue in acetic acid, digestion with pepsin and trypsin and extraction with saline solution. Finally the following method was accepted as the routine procedure: Fresh tumor tissue was placed in the mincing apparatus devised by Carpenter [8]; 0.1 cc. of the pressed juice thus obtained was mixed in a graduated centrifuge tube with 10 cc. of petroleum benzin U.S.P. The suspension was left standing for thirty minutes in the refrigerator; then the benzin was poured off and the sediment was mixed with 10 cc. of isotonic sodium chloride solution. The mixture was left in the refrigerator overnight (eighteen hours); then the tube was centrifuged at 3,000 revolutions per minute for thirty minutes. Four to six samples were taken from the supernatant fluid of each tube. A drop was placed with a micropipet on a collodium film supported on a 200 mesh wire screen. The sample was allowed to dry in the air and was kept in a desiccator over calcium chloride until ready for examination. The original micrographs were taken with

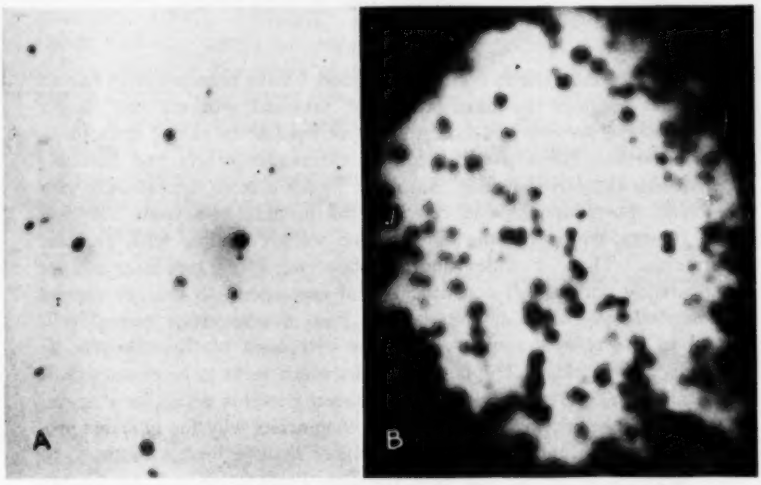

Fig. 2.—*A*, melanoma (case 19); single globules of large diameter together with smaller globules; pepsin digestion extract. *B*, ovarian carcinoma (case 6); large globules, single and in short chains.

These electron micrographs were taken at a magnification of 5,000 diameters and photographically enlarged 4 times, so that the final magnification is 20,000.

an RCA electron microscope on Eastman contrast lantern slides at a magnification of 5,000, and the negatives were studied in a Spencer microfilm reader, which magnifies fifteen times. Thus a total magnification of 75,000 diameters was obtained.

OBSERVATIONS

The table summarizes the electron-microscopic observations together with the histologic diagnosis, the age and the sex of each patient.

Globular bodies were noticed in most extracts of tumors, whether these were cancerous or benign. Their diameter ranged from 20 to 160 millimicrons. They

8. Carpenter, E.: Science **106**:621, 1947.

were spherical, and in most of the extracts they were well separated from one another. In several specimens, clusters, short chains and larger aggregates were present. There was a definite difference in size between cancerous and benign tumors. As a rule the size of the globules was larger in cancer tissues than in benign tumors. While in extracts of benign tumors the particles seldom exceeded 60 millimicrons, in extracts of cancer tissue they often exceeded 80 millimicrons. The fact that one did not encounter globules as large as those described by Porter and co-workers and also by Gessler and Grey can be explained by the difference of preparation. Both groups of investigators fixed their tissue with osmium tetroxide, which preserved the lipid fraction of the cytoplasmic globules, while in our method lipid linked to the protein was removed by treatment with benzin. The observation of the English authors that extracts of tumors of mice of high cancer strains contain particles measuring only 20 millimicrons is probably also due to the difference in preparation of the extract. Trypsin and a Berkefeld filter will certainly remove all larger globules from the tumor extracts.

COMMENT

While results which my associates and I have obtained with human material confirm the observations of previous workers that larger globules are present in cancer tissue, we hesitate to accept their interpretation that these particles are of extraneous origin and probably virus-like causative agents. Since we [9] were able to demonstrate very similar spherical bodies in cerebrospinal fluid from persons who had no tumors, we are of the opinion that we are dealing with globular proteins. Those globules under a diameter of 60 millimicrons are apparently normal cell constituents and correspond to the microsomes described by Porter and co-workers [10] in noncancerous animal cells and to the *spherules* observed in the cytoplasm of thrombocytes by Bassis and Bricka.[11] The large globules which seem to be characteristic of cancer cells are also very likely globular proteins which have aggregated to large micelles. The question then arises why the globular proteins appear in much larger size in cancer than in benign tissue.

It seems to us that the most plausible explanation is a disturbance in the colloidal state of the cytoplasm of cancer cells. Several physicochemical and experimental observations point in this direction. Cowdry and Paletta [12] demonstrated by ultracentrifuge studies that cancer cells have a lower viscosity than normal cells. Cramer [13] found that cancer cells contain relatively more water than normal tissue and that their water content increases directly with the growth rate of the particular tumor as measured by the mitotic index.

9. Hellwig, C. A.; Drake, R. L.; Voth, H. W., and Bleicher, J. E.: Am. J. Clin. Path. **18**:852, 1948.

10. Porter, K.; Claude, A., and Fullam, E. F.: J. Exper. Med. **81**:233, 1945.

11. Bassis, M., and Bricka, M.: Biochim. et biophys. acta **2**:239, 1948.

12. Cowdry, E. V., and Paletta, F. X.: Am. J. Path. **17**:335, 1941.

13. Cramer, W. J., cited by Cowdry.[1]

Also of interest is Spek's[14] experimental observation that the rate of reproduction of Balantidium can be increased twenty times by adding lithium chloride to the culture medium, which causes swelling of the cytoplasm of the protozoa. While no definite chemical differences have been demonstrated[15] in the proteins of cancerous and normal cells, marked differences in vital phenomena can apparently be created by different associations and linkages of the cell constituents. The large size of the globular proteins in cancerous cells is very likely an expression of some peculiarity in the colloidal state of the cell.

CONCLUSIONS

Extracts of 23 cancerous and 7 benign human tumors were studied with the electron microscope. Spherical bodies were observed in most tumor extracts, benign as well as cancerous. There was a definite difference in the diameters of these globules, the particles found in cancer extracts being larger than those in benign tissue.

In our opinion these globules are not virus-like causative agents of cancer, but globular proteins. The small spherical bodies are normal cellular constituents, while the larger particles are probably aggregates of the cytoplasmic globules due to an alteration in the colloidal state of the cancer cell.

14. Spek, J., cited by Ostwald, W.: Die Welt der vernachlässigten Dimensionen, Leipzig, Theodore Steinkopff, 1921, p. 142.

15. Toennis, G.: Cancer Research **7**:193, 1947.

LEAD POISONING DIAGNOSED BY THE PRESENCE OF NUCLEAR ACID-FAST INCLUSION BODIES IN KIDNEY AND LIVER

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NOT ONLY viruses but other agents may lead to the production of cellular inclusion bodies. Inclusion bodies may occur after the ingestion of certain metallic compounds, e. g., lead (Blackman [1]) or bismuth (Pappenheimer and Maechling [2]), and after the injection of aluminum and ferric compounds (Olitsky and Harford [3]). Inclusion bodies caused by bismuth or lead are acid fast when stained with the Ziehl-Neelsen technic. This property may serve as a useful guide for their further identification.[4]

The finding of inclusion bodies may shed light on the disease underlying an otherwise unexplainable death. The following report of a case elucidates this point.

REPORT OF CASE

A 21 month old boy was admitted to St. Catherine's Hospital with a history of increasing irritability of four weeks' duration. Ten hours prior to admission he had vomited profusely. He had always been difficult to manage and was in the habit of placing in his mouth everything that he could put his hands on. He had a normal neonatal period with normal growth and development. On admission he appeared to be dehydrated and was pale, drowsy, irritable and uncooperative. There was a systolic murmur over the mitral region of the heart; the heart rate was 140. The lungs were clear to percussion and auscultation. The abdomen was scaphoid and soft, without abnormal changes. The body temperature was 102 F. The pupils reacted to light, and there was normal accommodation reaction. Flexion of the neck produced some pain. There were a moderately pronounced Brudzinsky sign, an equivocal Babinski sign on the right and a Kernig sign on the right. There was no tenderness of the muscles of the back, and no paresis or paralysis. The cranial nerves were intact. A spinal tap was attempted, but owing to the irritability of the child, only spinal fluid mixed with blood was obtained. The urine showed a specific gravity of 1.020, with acetone (1 plus), 1 to 2 white blood cells and a few epithelial cells. A blood count revealed 2,800,000 red cells. The hemoglobin amounted to 6.3 Gm. per hundred cubic centimeters (42.4 per cent). There were 10,000 white blood cells, of which 50 per cent were segmented

From the Department of Pathology, St. Catherine's Hospital.

1. Blackman, S. S., Jr.: Bull. Johns Hopkins Hosp. **58**:384, 1936.
2. Pappenheimer, A. M., and Maechling, E. H.: Am. J. Path. **10**:577, 1934.
3. Olitsky, P. K., and Harford, C. G.: Am. J. Path. **13**:729, 1937.
4. Wachstein, M.: Am. J. Clin. Path. **19**:608, 1940.

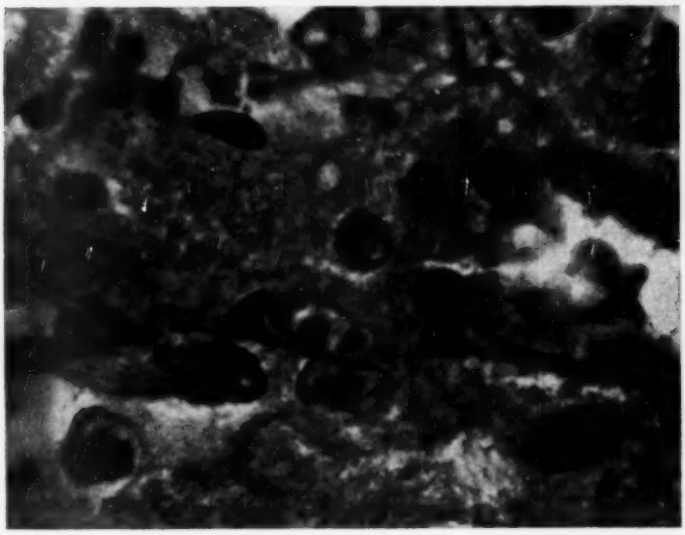
neutrophilic leukocytes, 3 per cent band cells, 40 per cent lymphocytes and 6 per cent monocytes. There was considerable hypochromasia, poikilocytosis, anisocytosis and moderate basophilic stippling of red cells. Five rubricytes were found for 100 white cells. The reticulocyte count was 12 per cent; the thrombocyte count, 270,000. Serum protein was 6.35 Gm. per hundred cubic centimeters, with globulin 1.95 Gm. and albumin 4.4 Gm. The ascorbic acid level was 1.3 mg. per hundred cubic centimeters of plasma. The Kahn reaction of the blood was negative.

The child was given 2.5 per cent dextrose solution in lactated Ringer's solution U. S. P., but he did not improve. In the following hours spasm of the neck increased. There was tenderness over the posterior region of the thighs. In reaching for water the child seemed to be ataxic. On a second spinal tap, eleven hours after the first, clear fluid under pressure was obtained, containing 25 white cells per cubic millimeter. The total protein was markedly increased to 258 mg. per hundred cubic centimeters. Sugar was 100 mg., chlorides 659 mg., per hundred cubic centimeters. A culture of the fluid remained sterile. During the next few hours the condition became progressively worse. The child lapsed into deep coma, spasm of all extremities developed and death followed twenty-four hours after admission.

Necropsy (ten hours after death).—The body was that of a 21 month old white boy in good nutritional state. The mucous membranes and the skin were pale. The abdominal cavity did not contain any increased amount of fluid. The serosal surfaces were smooth and glistening. The pleural cavities contained no excess of free fluid, and there were no adhesions. The heart was slightly enlarged and weighed 80 Gm. (normal, 56 Gm.). The pericardium was smooth and glistening. The myocardium was flabby and pale. All chambers of the heart were somewhat dilated. The valves were competent. The coronary arteries and the aorta were not unusual. The lungs were heavier than normal and weighed 380 Gm. (normal, 155 Gm.). On cut section they oozed a fair amount of frothy edema fluid and dark red blood. The liver was enlarged and weighed 600 Gm. (normal, 350 Gm.). The outer surface was smooth and dark red. On cut section it oozed a fair amount of dark red blood. The structure was indistinct. The spleen was enlarged and weighed 65 Gm. (normal, 33 Gm.). The cut section was dark purple and congested. Both kidneys were similar and weighed 120 Gm. together (normal, 90 Gm.). The capsules stripped with ease, revealing a smooth outer surface. The cut section appeared somewhat congested. The proportion between the cortex and the medulla was normal. The pelves, ureters and bladder were not unusual. Cross sections of lumbar and thoracic vertebrae revealed moist, pale, red marrow. The brain was somewhat edematous, and at the base the vessels appeared congested. The meninges did not appear unusual. Coronal sections of the brain did not reveal any significant gross changes.

Microscopic Examination.—Cross section of the heart showed foci of lymphocytic and plasmacytic infiltration as well as occasional proliferation of myocytes. In some areas fibroblastic proliferation with some damage of muscle fibers was noticed. The lungs showed marked edema and congestion. There was also considerable accumulation of lymphocytes and plasmacytes in the walls of the bronchi. The liver showed definite fatty changes and moderate congestion. In preparations stained with sudan III and sudan black, almost each liver cell revealed one or several large fat droplets. Some of the nuclei of the liver cells contained eosinophilic inclusion bodies. These were mostly round and occasionally had a somewhat irregular outline. The nuclei of the liver cells were not significantly changed. The spleen showed considerable increase in the cellularity of Billroth's

cord. There was an increase in the numbers of plasmacytes and eosinophilic leukocytes. The kidneys on section revealed innumerable nuclear inclusion bodies in the cortex and in the subcortical zone (figure). They occurred in tubules that could be identified as proximal convolutions but also in tubules forming the medullary rays. Nearly all these inclusion bodies were eosinophilic in sections stained with hematoxylin-eosin. They were round or irregular and varied in size from tiny droplets to some larger than the nuclei. One or several inclusion bodies were found in one nucleus. Apart from the swelling of the nuclei there were only slight degenerative changes in the cytoplasm of the tubules. The inclusion bodies stained orange with the Masson stain as modified by Pollak [5] and proved to be acid fast. No appreciable fat was detected with the sudan stain (sudan III



Section of kidney stained with hematoxylin-eosin. Several nuclear inclusion bodies are seen. × 897.

and sudan black) in the tubular epithelium. Paraffin sections were made from various areas of the brain and stained with hematoxylin-eosin. In addition, celloidin sections were prepared and stained by the Nissl technic with the aid of Dr. H. M. Zimmerman, Montefiore Hospital, Bronx, N. Y. The appearance of the meninges was normal. There were a few small foci of glial proliferation in the subpial layer of the cortex. The remainder of the cortical layers and the subcortex were not remarkable. No alteration of blood vessels was seen. In the cerebellar sections, a few glial nodules occurred in the molecular layer. They were sometimes associated with dropping out of a few nearby Purkinje cells. The loss of these cells, while not extensive, was definite and widespread. The

5. Pollak, O. J.: Arch. Path. **37**:294, 1944.

blood vessels were normal in appearance. The medulla at the level of the olive revealed no abnormalities. Cross section of other organs did not reveal any other significant changes.

Chemical Test.—In 10 Gm. composite samples of kidney and liver fixed in formaldehyde solution 1.5 mg. of lead was found in 100 Gm. of tissue (highest amount of lead found in control tissue, 0.05 mg. per hundred grams) by Dr. A. O. Gettler, Medical Examiner's Office, New York.

Anatomic Diagnosis.—Lead poisoning with typical inclusion bodies in kidneys and liver; minimal gliosis and loss of Purkinje cells of the brain; focal subacute myocarditis; congestion and edema of the lungs; congestion of liver, spleen and kidneys; severe fatty changes of the liver; chronic bronchitis.

COMMENT

The case is of special interest because of the nuclear inclusion bodies in the liver and the kidneys which furnished the clue to the explanation of a death that would otherwise have remained obscure. There was nothing in the history of the child that suggested the possibility of lead poisoning. Questioning of the parents, however, after the postmortem diagnosis had been established, revealed the fact that the child was in the habit of putting various objects into his mouth. The child had considerable anemia with increased numbers of reticulocytes and a number of nucleated blood cells in the peripheral circulation. There was also moderate basophilic stippling of red cells. This finding was not considered significant for lead poisoning, since basophilic stippling is not infrequently seen in patients who have anemia due to other causes. The increased number of stippled red cells is of much higher significance in the absence of an appreciable anemia.[6] A lead line on the gum was not found. A roentgen examination of the long bones was not made; however, no significant changes were seen in the ribs on a routine roentgenogram of the chest.

The spinal fluid was typical for lead poisoning. It must be kept in mind, however, that similar spinal fluid changes are found in other diseases. In lead poisoning a spinal tap yields clear fluid under increased pressure with increased protein content and often pleocytosis.[7]

Although the predominant clinical symptoms were of a cerebral nature, microscopic examination of the brain did not reveal changes which could be considered typical for lead encephalopathy. Lead injury leads to swelling of the vascular epithelium, perivascular and diffuse edema and hyperplastic changes in the leptomeninges as well as to damage of nerve cells and to neuroglial alterations.[8] It was the opinion

6. Belknap, E. L.: J. A. M. A. **139**:818, 1949.

7. Kirchner, E.: Deutsche med. Wchnschr. **68**:351, 1942. Bowne, I. B.: J. Nat. Med. **36**:187, 1944.

8. Kelaitis, A.: J. Nerv. & Ment. Dis. **93**:313, 1941.

of Dr. H. M. Zimmerman (chief, Laboratory Division, Montefiore Hospital, Bronx, N. Y.) that the changes seen in this case were compatible with but by no means characteristic of lead encephalopathy.

The microscopic changes in the other organs with the exception of the nuclear inclusion bodies were nonspecific. Focal interstitial myocarditis is frequently encountered not only in infectious diseases but in many other pathologic states.[9]

Inclusion bodies such as those seen in this case were first described by Blackman,[1] who found them in each single case at 21 necropsies of children who died of lead poisoning. Identical inclusion bodies were repeatedly described in experimental lead poisoning.[10]

If proper methods are used, the inclusion bodies can be detected easily. They may, however, be overlooked on superficial examination, particularly if, as in the case described here, degenerative changes of the tubular epithelium are scanty. This may explain the fact that the presence of inclusion bodies was not referred to in several recent reports of cases of lead poisoning in which postmortem examination had been done.

The inclusion bodies stain prominently with Pollak's modification of the Masson stain as suggested by Gorham [11] for the detection of distemper inclusion bodies. Their acid-fastness furnishes a valuable clue as to their probable nature, since among various inclusion bodies only those caused by lead and bismuth proved to be acid fast.[4] The morphologic aspect of the bismuth inclusion bodies is, however, so different that their distinction should be made without difficulty. The final proof, of course, has to be established by the chemical examination of the tissues for lead.

SUMMARY

The cause of death in a 21 month old boy was clarified by the finding of nuclear inclusion bodies in the liver and the kidneys. On the basis of their morphologic aspect and acid-fastness the inclusions were assumed to be caused by lead. Chemical examination of kidney and liver tissue confirmed this assumption. The significance of nuclear inclusion bodies for the diagnosis of lead poisoning is stressed.

9. Saphir, O.: Arch. Path. **32**:1000, 1942; **33**:88, 1942. Fawcett, R. M.: ibid. **45**:25, 1948.

10. Finner, L. L., and Calvery, H.: Arch. Path. **27**:433, 1939. Diaz-Rivera, R. S., and Horn, R. C., Jr.: Proc. Exper. Biol. & Med. **59**:161, 1945. Dalldorf, G., and Williams, R. R.: Science **102**:668, 1945. Wachstein.[4]

11. Gorham, J. R.: Science **107**:175, 1947.

HISTOGENESIS OF BASAL CELL CARCINOMA

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AND
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A PREVIOUS study of epithelial tumors of the skin was made during the ten year period from January 1939 to January 1949, which included 984 such tumors. During the course of the study 182 tumors diagnosed as basal cell carcinoma were included in the series. Because conclusions were reached which seemed to be incompatible with those expressed in recent studies of the histogenesis of the basal cell carcinoma,[1] it was deemed advisable to carry on a further study of this type of tumor to determine whether or not present concepts of the histogenesis of the basal cell carcinoma are valid. The conclusions derived from this study corroborated the older concepts first suggested by Krompecher.

HISTORICAL REVIEW

Basal cell carcinoma of the skin was first described by Jacob, in 1827, whence the eponym jacobian ulcer was derived. It was recognized as a slowly growing, invasive, ulcerating but nonmetastasizing tumor of the skin. However, an accurate pathologic study of this tumor was not made until 1900, when Krompecher[2] described 21 cases and attempted to group them according to four types of growth. This classification is of interest as it forms the basis of most subsequently suggested arrangements and is as valid at the present time as when it was suggested. Krompecher divided them into (1) cases of a solid pouchlike downgrowth of epithelium, (2) cases of an epithelial mass containing cysts, (3) cases of a glandular form made up of interlacing strands of epithelial cells and (4) cases in which nests of epithelium formed parakeratotic pearls.

However, in 1902 Krompecher expanded his concept of basal cell carcinoma to include tumors occurring in the mucous membranes of mouth, nose, pharynx, larynx, esophagus and vagina. Histologists

From the Department of Pathology of Passavant Memorial Hospital and Northwestern University Medical School.

1. Foot, N. C.: Am. J. Path. **23**:1, 1947.

2. Krompecher, E.: Beitr. z. path. Anat. u. z. allg. Path. **28**:1, 1900.

now know that while these tumors are histologically similar to basal cell carcinoma they are biologically more malignant, being undifferentiated squamous cell carcinoma, and should not be included in the category of basal cell carcinoma.

Mallory [3] demonstrated fine longitudinal epithelial fibers in basal cell carcinoma, which he believed were identical with those found in embryonic hair follicles. He therefore concluded that this type of carcinoma arose from the hair matrix, including the sebaceous and sweat glands. This work, however, received little attention, and the theory prevailed that the basal epithelium of the epidermis was the site of origin of the basal cell carcinoma.

Paul,[4] in his observations on the origin, cause and treatment of rodent ulcer in Australia, adhered closely to the original concept of Krompecher and suggested four types: (1) a reticular type, in which the growth is composed largely of strands of cells enclosing a stroma, a growth in which cystic structures may be formed; (2) a budding type, in which a solid type of growth occurs, showing budding or finger-like projections; (3) a combined reticular and budding type; (4) a basal cell type. Paul expressed the belief that the first three types represented growths whose origin lies in the pilosebaceous apparatus, the normal site of which is in the corium, and are the least malignant of the types named. The fourth type was due to a proliferation of the epidermis. He stressed the effect of actinic rays in causing rodent ulcer.

Haythorn [5] made the first careful study of the histogenesis of the so-called basal cell carcinoma. In a study of 139 specimens, he found that all conformed to the characteristics suggested in Krompecher's classification and that all varieties were included. It was unusual to find a single tumor which did not include more than one of Krompecher's types. In an exhaustive study of the staining characteristics of the tumor cells and of the basement membrane, he reached the conclusion that they all originate from hair matrix. Thus, there are commonly found more or less perfectly formed hair shafts in the basal cell tumor. Silver staining technics show the type of basement membrane to be similar to that around the hair follicle. The distribution of pigment in a basal cell carcinoma he considered as equivocal evidence of the tumor's origin. He expressed the belief that sebaceous glands frequently form basal cell tumors but that sweat glands do not take part. The apparent continuity of the tumor masses with the basal layer of the epidermis, he concluded, was only apparent.

3. Mallory, F. B.: J. A. M. A. **55**:1513, 1910.

4. Paul, N.: M. J. Australia **1**:85, 1923.

5. Haythorn, S. R.: Am. J. Cancer **15**:1969, 1931.

The difficulty of accepting the basal layer origin of these tumors was due primarily to the concept of differentiation of the basal layer of cells. The normal basal layer, when it differentiates, forms large prickle cells which are totally unlike the basal carcinoma cells. Krompecher claimed that the cells of the tumor were basal cells which had retained their embryonic structure and did not differentiate like skin, and therefore did not take the form of prickle cells. Haythorn expressed the opinion that if this were so, then the basal cell carcinoma, being derived from embryonic cells, should retain the characteristics of other tumors derived from embryonic cells; that is, they should be highly malignant. This is not true, however, the basal cell carcinoma being cancerous to only a low degree. Haythorn attempted to explain this discrepancy by deriving it from the hair matrix, in which location differentiation is away from the formation of prickles and toward the formation of longitudinal fibers. He therefore derived basal cell carcinoma from the pilosebaceous apparatus, rejecting any evidence that the tumor tissue is continuous with the basal layer of the epidermis as being only apparent.

At the time that Haythorn's work appeared in print, Niles[6] published a report of metastases derived from a basal cell carcinoma. This report is mentioned only to say that the illustrations are typical of a squamous cell type of growth and must be rejected. Numerous reports of metastasizing basal cell carcinoma have been published,[7] but none of them pass the test of close investigation.

Montgomery,[8] in a study of the histogenesis of the basal cell carcinoma, grouped the tumors according to two forms: (1) the benign form (epithelioma adenoides cysticum and cylindroma), which may arise from multiple points of origin, that is, from the basal cells of the epidermis, from the basal cells of the outer sheath of the hair follicle, from the sebaceous gland and the sweat gland; (2) the malignant form, which may rarely arise from the hair matrix, more often from the basal cells of the outer root sheath of the hair follicle but most often from single or multiple points of origin in the basal layer of the epidermis. Montgomery determined that silver stains were not of value in distinguishing a tumor of basal cell origin from a tumor arising in a hair matrix. Melanin formation likewise did not indicate the origin of the basal cell growth. He likewise concluded that the occurrence of a mixed basal cell–squamous cell carcinoma represents

6. Niles, H. D.: Am. J. Cancer **15**:2341, 1931.

7. Finnerud, C. W.: J. A. M. A. **82**:775, 1924. De Navasquez, S.: J. Path. & Bact. **53**:437, 1941. Spies, J. W.: Arch. Surg. **21**:365, 1930. Small, C. S., and Hankins, F. D.: Arch. Path. **47**:196, 1949.

8. Montgomery, H.: Radiology **25**:8, 1935.

a metamorphosis from basal to squamous cells and decried the concept of a fundamental and separate histogenesis.

About this time a theory of the histogenesis of basal cell carcinoma was suggested by Glasunow [9] and supported by McFarland, Ciccone and Gelehrte.[10] In an investigation of 254 cases of basal cell carcinoma of the face, Glasunow was convinced that the distribution of the lesions so closely corresponded with the position of the "facial fissures," or intervals between the various embryonal fissures or buds, through whose final concrescence the face is formed, as to prove that the tumors are of embryonal origin, that is, dysontogenetic. He called them facial fissure carcinoids or skin carcinoids. However, he was unable to explain the genesis of tumors found in locations other than the face.

Warren, Gates and Butterfield [11] studied 321 cases in an attempt to correlate the histologic type with clinical behavior. They divided the series into five types: (1) basal cell carcinoma; (2) basal cell carcinoma with foci of keratinization; (3) mixed "basosquamous" carcinoma; (4) hair matrix carcinoma; (5) cystic basal cell carcinoma. In their study they frequently found the tumor to be multicentric in origin, growing from several distinct points of the overlying epidermis and occasionally from skin appendages. The cystic type they held to be the result of degeneration of either tumor or stroma. In their study of five year cures following irradiation, the percentages given are: type 1, 41 per cent; type 2, 20 per cent; type 4, 33 per cent; type 5, 100 per cent. They concluded that development toward a basal cell or a hair matrix tumor denotes low malignancy, while differentiation toward a squamous cell carcinoma is present in the more dangerous tumors.

Gaté, Massia and Delbos,[12] in a discussion of pigmented basal cell epithelioma, cited the incontestability (in their opinion) of the theory that the basal cell tumor takes origin from the pilar structures, the sebaceous glands and sometimes even the sudoriferous glands. They stated that the hypothesis establishing a relationship between the basal cells of the epidermis and the cells of the basal cell carcinoma ought to be abandoned. They found an incidence of pigmented forms of 6 to 10 per cent. These have the same prognosis as the ordinary type, and the course and the mode of therapy are not altered. The authors stressed the importance of differential diagnosis respecting these tumors

9. Glasunow, M.: Frankfurt. Ztschr. f. Path. **46**:140, 1933.

10. McFarland, J.: Ciccone, E. F., and Gelehrte, J.: Am. J. Cancer **25**: 273, 1935.

11. Warren, S.; Gates, O., and Butterfield, P. W.: New England J. Med. **215**: 1060, 1936.

12. Gaté, J.; Massia, G., and Delbos, J.: Ann. de dermat. et syph. **8**:337, 1937.

and cancerous melanoma, a tumor which carries a much graver prognosis.

Holtzman and Bolker [13] suggested an interesting and unusual theory to explain the peculiar biologic behavior of the basal cell carcinoma. They fostered the concept of the basal layer as being a continuous protoplasmic mass containing nuclear elements. This continuity diminishes as the prickle layer is reached. By microdissection, the prickle cells can be separated with ease, while the basal cells can be separated only with difficulty. In the basal cell carcinoma the same continuity of protoplasm exists, retains connection with the point of origin of the epidermis, as proved by serial sections, and explains lack of metastases. Although attractive, this theory is untenable since intercellular bridges may be present in the basal layer, according to most authorities, and can frequently be demonstrated in the cells of the basal cell carcinoma. These authors explain the formation of basal cell carcinoma by stating that the cells proliferate in one direction corresponding to the polarity of the ancestral basal cell at the time it underwent mutation.

Krompecher, in his original work, included so-called basal cell carcinoma of the oral, laryngeal, pharyngeal, nasal, esophageal and vaginal mucous membranes. Owen [14] made a thorough study of 836 lesions of mucous membranes diagnosed as carcinoma to determine the incidence of basal cell growths in these areas. None were found. The growths usually mistaken for basal cell carcinoma are pathologically and clinically highly invasive squamous cell carcinoma. At the present time the exclusively cutaneous origin of the basal cell carcinoma is accepted by practically everyone.

The recent work of Foot [1] has redirected attention to the pilosebaceous apparatus as the point of origin of the basal cell carcinoma. Foot devised an elaborate system of classification of these tumors depending on the points of origin of the growths.

1. Pilar type, derived from the hair matrix. The overlying epidermis is intact, atrophic and, in the late stages, ulcerated.
   - (*a*) Pilar type proper, imitating the structure of the hair follicles.
   - (*b*) Primordial type, forming large spherical masses of cells.
   - (*c*) Cylindric cell or ribbon type, rarely encountered.
   - (*d*) Cystic type, a variant of *a* and *b*.
2. Sudoriparous glandular type.
   - (*a*) Adenoid type.
   - (*b*) Hydradenomatous type, either resembling the solid hydradenoma or the papillary cystic hydradenoma.
3. Basal cell type, uncommon. Foot considered this type to be more properly a plexiform epidermoid carcinoma.

13. Holtzman, I. N., and Bolker, H.: Am. J. Roentgenol. **47**:463, 1942.
14. Owen, M.: Arch. Path. **10**:386, 1930.

With the technic of impregnating neurofibrils with silver (Nonidez' modification of the Ramón y Cajal method) Foot demonstrated plexuses of prominent and readily visible nerve filaments in the pilar papillae and about the sebaceous glands. Very few such fibrils were demonstrated in the papillae of the normal dermis or in the basal layers of the epidermis. In adnexal carcinoma, there are heavy bundles of nonmyelinated fibers running in the stroma. This the author interpreted as an implication that the adnexal carcinoma was related to hairs, sebaceous glands and sudoriparous glands rather than to basal elements of the epidermis. Foot reiterated the theory of the hair matrix origin of the basal cell carcinoma suggested by Haythorn and agreed with the latter in almost every particular. He also insisted that the contact of masses of basal cells with the basal layer of the epidermis is only apparent and demonstrated this to his own satisfaction by means of serial sections of early basal cell lesions and construction of wax models. He denied the basal cell origin of the lesion and suggested the name originally introduced by Haythorn, "adnexal carcinoma," to include all forms of basal cell carcinoma.

Willis [15] insisted on the multicentric origin of basal cell carcinomas, from the epidermis itself, from the pilosebaceous apparatus and from the sweat glands, either singly or in combination. He used a simple classification: superficial basal cell carcinoma, derived from the basal layer of the epithelium, and subepidermal basal cell carcinoma, derived from the adnexae. In his own words:

> . . . Studies of early superficial basal cell tumors show unmistakably that these often arise, not from single minute foci, but from multiple foci in considerable areas of epidermis, and that the basal cells of hair follicles and shafts and of the skin glands may also participate in the cancerous change.

In a discussion of the presence of nerves he expressed the belief that there is no convincing evidence that cancer cells are innervated, that all genuine nerves observed in tumors are inclusions and the supposed nerve endings in tumor cells are only retraction bulbs or varicose nerve fibers contiguous with the cells. Nerves show a remarkable persistence in the substance of invading tumors, so that all relationships of residual nerve fibers and tumor elements will be demonstrated. In addition, when a nerve trunk is damaged by a tumor, numerous new fibrils grow from the lining axis-cylinders of the proximal stump of the nerve trunk. These new axis-cylinders not only grow within the perineural tube of the proximal portion but penetrate into the neoplastic tissue. If this concept is valid, the fact that nerve fibers are present in the masses of basal cells as demonstrated by Foot is no particular indication that these cells originate from the pilar

15. Willis, R. A.: Pathology of Tumors, St. Louis, C. V. Mosby Company, 1947.

papillae and sebaceous glands. Their presence merely indicates the fortuitous circumstances that proliferating neurofibrils of the surrounding damaged or irritated nerve bundles have infiltrated the tumor.

The generally accepted nonspecificity of the silver impregnation method of demonstrating nerve fibers is likewise another factor in weakening the validity of the work of Foot.

MATERIAL AND METHODS

In the present study there are 182 examples of the basal cell type of carcinoma, occurring in 166 patients. There was 1 patient with two simultaneously occurring lesions of this type. Fifteen of the specimens represented recurrences. Three patients had a coexistent but distinct squamous cell carcinoma. The tumors are first tabulated as to general histologic type (table 1). Of the total number of epithelial tumors of the skin studied, 18.5 per cent represented basal cell carcinoma.

The classic description of the basal cell carcinoma invariably includes its distribution as being preponderantly localized to an area of the face bounded by the hair line, the ears and the upper lip. That it may occur on almost every part of the body is readily seen in table 2. Assuming that those lesions listed

TABLE 1.—*Tumors Grouped According to Histologic Types*

	Number	Percentage
Basal cell carcinoma	182	100
"Basal cell" type	150	82.4
Mixed basosquamous type	25	13.7
Pigmented basal cell type	6	3.2
Mixed pigmented basosquamous type	1	0.7

under "face" and "unclassified" are present in the classic location, 31, or 17 per cent, of the total are present in another part of the body. The importance of this atypical distribution has rarely been emphasized in any large series.

In an attempt to prove the worth of Foot's classification of adnexal carcinoma, the 182 examples were carefully studied and tabulated (table 3). It was evident from the beginning that many of the specimens contained elements of several different types and that it was unusual for any single one to be listed under any single type. Although classification according to a number of different types based on histologic characteristics is valid in a descriptive way, the impression was gained that it added little to the final understanding of the histogenesis of the tumor, and was cumbersome.

In a preliminary survey of the material, sections stained with hematoxylin and eosin were examined, and the tumors were classified. Fifty-three, or 29.1 per cent, showed histologic evidence of origin from or continuity with the basal layer of the epidermis, either with or without evidence of simultaneous origin from appendages of the skin. This figure is undoubtedly low, since in many cases, if definite evidence of origin from the basal layer was not present in an ulcerated or advanced lesion, the tumor was placed in another category. Several early lesions had multicentric origins in both the basal layer and the pilosebaceous apparatus. In 1 case there was found incidentally in a section of skin removed for a squamous cell carcinoma a very small basal cell carcinoma, distinct from the squamous cell tumor. It showed definite evidence of originating from the basal layers.

TABLE 2.—*Distribution of Specimens of Different Types of Basal Cell Carcinoma**

Location	Basal	Mixed	Pigmented	Pigmented-Mixed
Temple	4	..	..	..
Forehead	12	1	1	..
Eyebrow	1	..	..	..
Eyelid	23	3	1	..
Ear	6	5	..	..
Cheek	13	3	..	..
Nose	22	4	..	..
Chin	4	..	..	..
Neck	7	..	..	1
Scalp	2	1	..	..
Lower jaw	2	..	..	..
Upper lip	12	1	..	..
"Face"	22	6	1	..
Thoracic wall	1	..	1	..
Nipple of breast	1	..	..	..
Back	6	..	..	..
Upper arm	2	..	..	..
Wrist	1	..	..	..
Dorsum of hand	3	..	..	..
Inguinal region	1	..	..	..
Thigh	2	..	..	..
Unclassified	4	1	2	..

* This tabulation is based on a total of 182 specimens obtained from 166 patients. Fifteen specimens represented recurrences. There was 1 patient from whom 2 specimens of basal cell carcinoma were simultaneously removed. There were 3 patients with coexistent basal and squamous cell carcinoma.

TABLE 3.—*Classification of Specimens of Basal Cell Carcinoma According to the Classification of Foot*

Type	Basal	Basosquamous	Pigmented	Pigmented-Mixed
Basal	7	1	3	..
Primordial	43	9	2	..
Pilar	5	1	..	..
Cylindric	2	..	..	..
Cystic	6	..	..	..
Adenoid	4	..	..	..
Hydradenomatous	4	..	..	..
Primordial-cystic	12	1	..	..
Primordial-pilar	4	1	..	..
Primordial-basal	24	5	..	1
Primordial-adenoid-cystic	1	..	..	..
Primordial-cylindric	3	1	..	..
Primordial-basal-cystic	7	2	1	..
Pilar-basal	6	1	..	..
Cystic-basal	3	..	..	..
Basal-cylindric	1	..	..	..
Basal-adenoid	1	..	..	..
Primordial-pilar-cystic	2	1	..	..
Primordial-pilar-cystic-basal	2	..	..	..
Pilar-adenoid	..	1	..	..
Primordial-adenoid	5	..	..	..
Primordial-pilar-basal	2	..	..	..
Cystic-cylindric	2	..	..	..
Primordial-pilar-adenoid	2	1	..	..
Pilar-cylindric	2	..	..	..

Specimens which were not ulcerated or which contained a definite inflammatory reaction were then selected for further study. These were stained with Masson's trichrome stain. Suitable small or histologically well preserved specimens were studied further by means of Wright's silver impregnation method. A few very small ones were selected for study by means of serial sections.

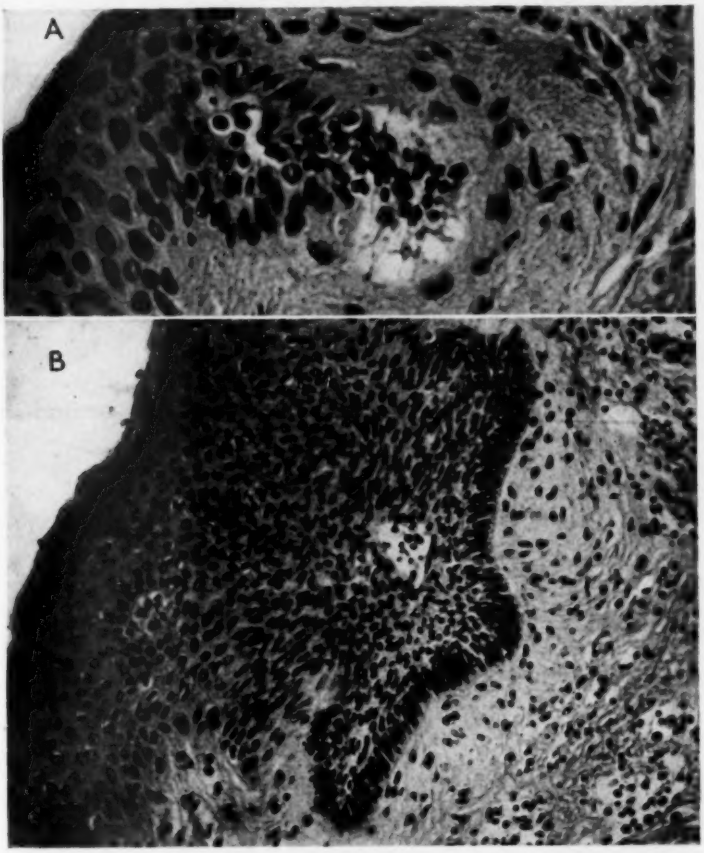

Fig. 1.—*A*, small satellite basal cell lesion extending for 100 microns. It originates from the basal layer of the epidermis. Case 10870; hematoxylin and eosin stain; × 260. *B*, satellite lesion showing gradual transition from the prickle cell layer to the mass of basal cells. The basement membrane is intact. Case 12803; hematoxylin and eosin stain; × 260.

RESULTS

The first and most striking characteristic of the basal cell carcinoma was its multicentric origin. In the great majority of specimens examined, with the pos-

sible exception of the very small ones, the multicentric origin was seen, the tumor cells arising from the sheath of the pilar apparatus, from the basal layer of the epidermis, occasionally from sebaceous glands and rarely from sudoriferous glands. This multicentric origin could be seen in the form of a tumor having isolated and independent points of origin in the basal layer, or arising from independent and separate pilar structures, or presenting any combination of these two. In one early lesion studied serially, although it was originally classi-

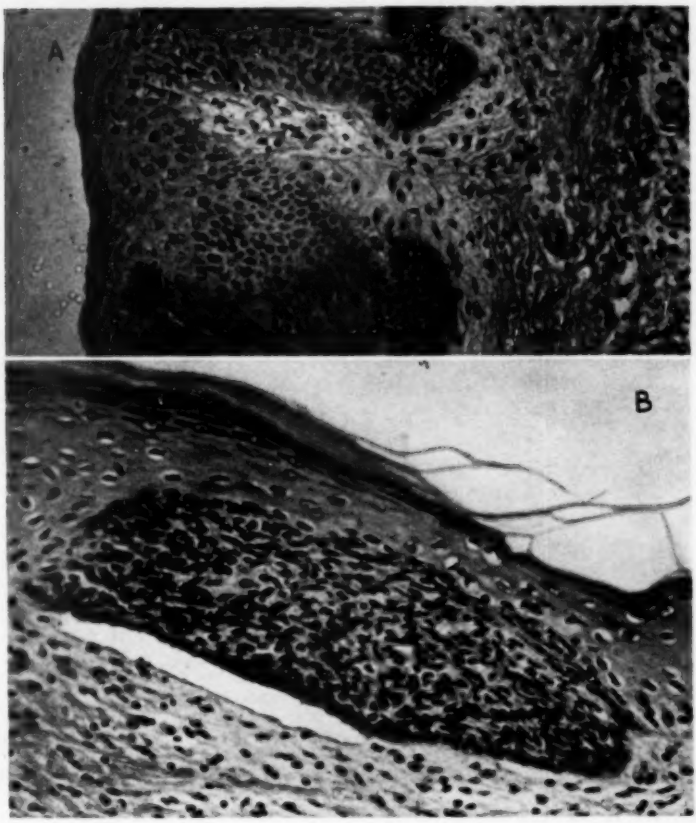

Fig. 2.—*A*, lesions similar to that in figure 1*B*. Serial sections showed absence of contact with hair follicles. Case 12803; hematoxylin and eosin stain; × 120. *B*, abrupt transition from the prickle cell layer to the mass of basal cells. The basement membrane in intact. The section contains no hair follicles but shows multiple similar foci of origin. Case 12803; Masson trichrome stain; × 240.

fied on preliminary examination as a tumor of the pilar type, small satellite foci originating from the basal layer were observed (case 10870). Another tumor on serial examination was found to have multiple widely separated and independent points of origin in the basal layer as well as multiple points of origin in the pilar structures (case 12803).

Foot [1] and Haythorn [4] denied that the masses of tumor cells were in any way continuous with the epidermis, explaining such a relationship as being only

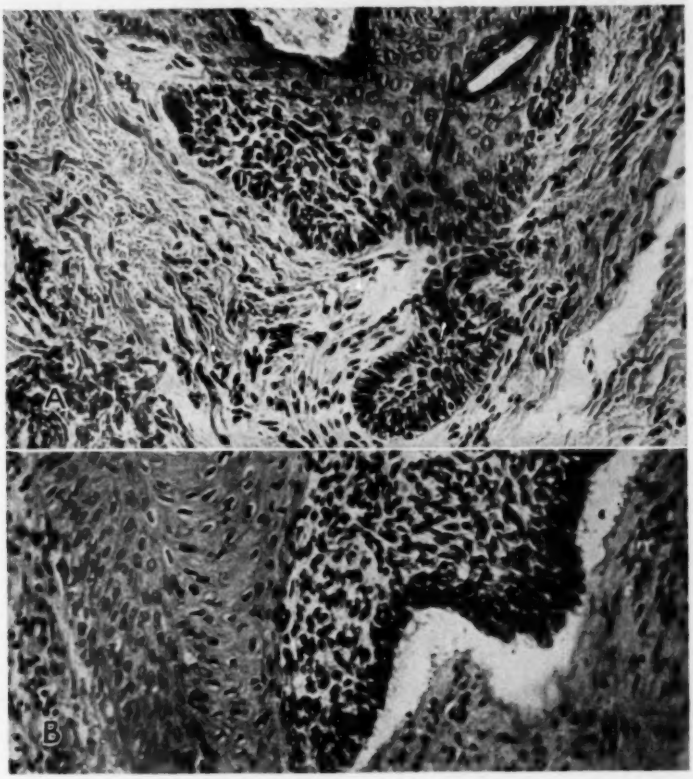

Fig. 3.—*A*, masses of tumor cells originating from the outer sheath of the hair follicle. Masson trichrome stain; × 180. *B*, focus of basal cell carcinoma originating from the outer sheath of the superficially located one third of a hair follicle. Hematoxylin and eosin stain; × 240.

apparent. This was not borne out in our studies. In the preliminary examination of hematoxylin-eosin preparations, the specimens were classified with reference to basal origin. Growths of this origin formed 29.1 per cent of the total number. Many of those which exhibited a basal origin were then examined with Masson's trichrome stain. It was established that cellular continuity was

actually present between the basal cell masses and the basal portions of the epidermis. Usually there was a rather abrupt transition between the two types of cells, but occasionally a gradual transition occurred. The basement membranes of the basal layer of the epidermis and the basal cell masses were continuous and uninterrupted. This was in marked contrast to the type of lesion in which upward expanding masses of basal cells actually encroached on the epidermis

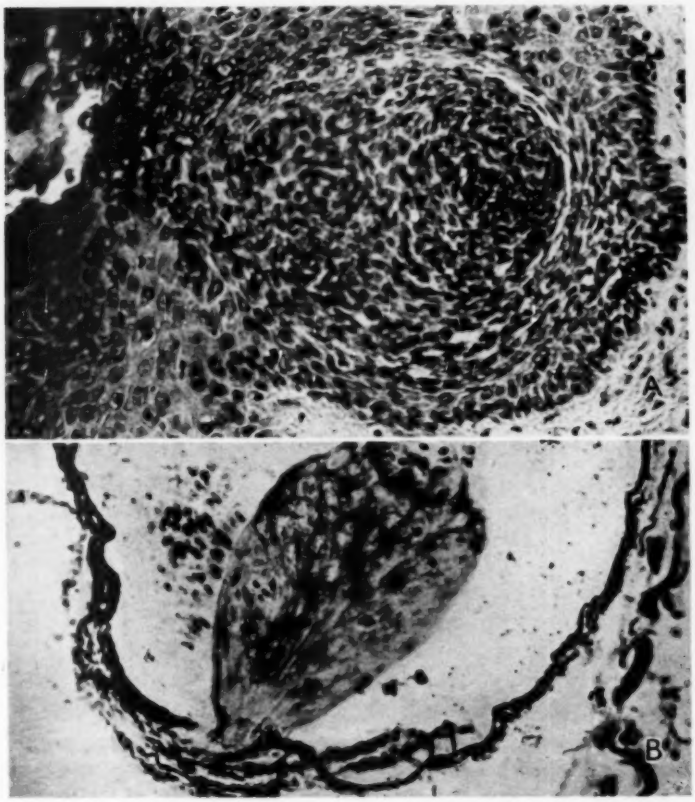

Fig. 4.—*A*, small intraepidermal focus of basal cell carcinoma found incidentally in an examination of squamous cell carcinoma, but independent of the latter, grade 1. Hematoxylin and eosin stain; × 120. *B*, hair matrix showing neurofibrils. Silver impregnation; × 240.

(subepithelial type of Willis). In the latter situation there was a very fine but recognizable layer of collagenous fibers between the upwardly expanding neoplastic tissue and the epidermis. The epidermis likewise was thin and appeared locally compressed.

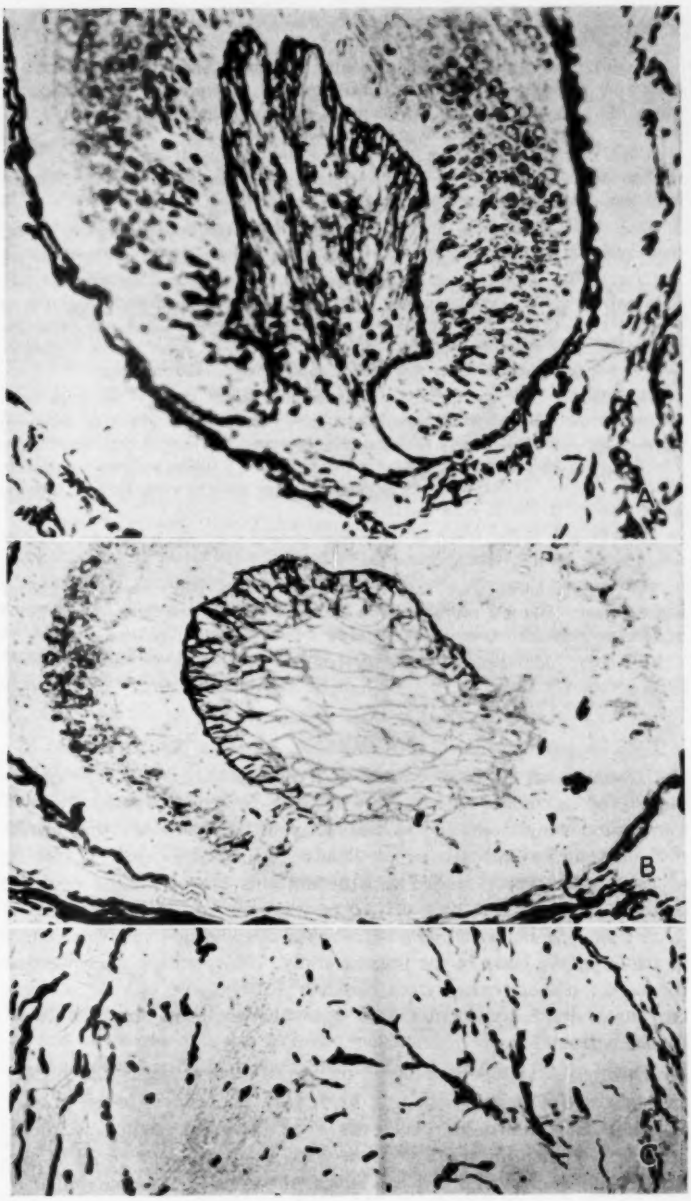

Fig. 5.—*A*, hair matrix showing neurofibrils. Silver impregnation; × 240. *B*, hair matrix showing neurofibrils; Silver impregnation; × 240. *C*, coarse neurofibrils in a focus of basal cell carcinoma. Note the haphazard distribution. Silver impregnation; × 240.

At this point it was decided that little or nothing new of value would be gained by a study of moderately small lesions. However, if the multicentric origin of the tumor was valid, a study of small satellite points of origin at the periphery of the lesion might give additional information. This proved to be true, and definite origin from the sheath of the pilar apparatus and basal layer was demonstrated in multiple small surrounding satellite foci. Several specimens were sectioned serially with interesting results.

Case 9707: There was multicentric origin from the external sheaths of the superficial one third of the hair shafts and from the basal layer of the epidermis.

Case 10870: This case was chosen as an instance of the pure pilar or subepithelial type. On serial section, there were multiple small foci of origin in the hair matrix, the upper portion of the sheath of the hair shaft and sebaceous glands and also multiple small foci of origin in the basal layer of the epidermis. One of the latter extended to a width of approximately 100 microns.

Case 12803: The specimen was a moderately large slightly ulcerated basal cell carcinoma. Serial study revealed multiple small foci of origin in the basal layer of the epidermis and in the sheath of the upper portion of the hair follicle. The deeper lying masses contained rudimentary hair follicles and were obviously pilar in origin. Three different sections of this tumor were studied serially, with identical results in each instance.

Case 14742: Serial study of the tumor showed multiple independent foci of origin in the basal layer and in the hair follicles.

Suitable specimens were studied by means of Wright's technic of silver impregnation. The fine neurofibrils in the pilar matrix were easily demonstrated in many sections. However, demonstrating similar fibrils in the neoplastic masses was much more difficult. In the majority of specimens these could not be demonstrated, and when present, they were distributed unevenly and haphazardly, so as to suggest a fortuitous occurrence.

COMMENT

It would not be incompatible with present day knowledge of the genesis of carcinoma to assume that there is a multicentric origin of the basal cell carcinoma in the basal layer of the epidermis, the sheaths of hair follicles and sebaceous glands. Morphologically the results of the present study tended to bear out this concept. The evidence that carcinoma of this type originates from the sudoriferous glands is much more inconclusive and a definite statement concerning this cannot be made on the basis of the present study. Morphologic evidence that the carcinoma originates from the hair matrix was lacking in most sections and the statement that it has such an origin must be based on inference.

Theories of histogenesis based on analogy are fraught with danger and must be accepted with reserve. That neurofibrils were present in the basal cell masses could easily be shown in some specimens. However, if their presence is to be used as a basis for proof of the pilar origin of the basal cell carcinoma, they must be demonstrated in all or at least in the majority of specimens. This could not be done in the present series. Studies of sections containing neurofibrils showed

an irregular and unorganized distribution, suggesting a fortuitous presence. This was emphasized by Willis, who explained that there was no convincing evidence that neoplastic tissue was innervated, that all relationships between residual nerve fibers and tumor elements could be demonstrated and that the presence of nerve fibrils indicated that a nerve trunk had been damaged by the tumor and that numerous fibrils were growing into the neoplastic tissue.

That the contact between masses of basal calls and the basal layer of the epidermis is only apparent was not borne out in the present study. Serial sections of small satellite lesions proved conclusively that the neoplastic tissue originated solely from the basal layer without any possibility of contact with adnexal structures. Histologically, the differentiation between a neoplasm having an actual origin in the basal layer and an underlying expansile mass of neoplastic cells encroaching on the basal layer was relatively simple. This was true of hematoxylin and eosin preparations as well as of those stained with Masson's trichrome stain. The lack of disruption between the basement membrane of the basal layer and that of the tumor masses corroborates this point.

An interesting study was carried out by Hoffman.[16] In a statistical analysis of the rates of growth of the cells of various strata of the epidermis, he found that the ratio of the rate of growth of spinous cells to that of basal cells is 3:1. This is similar to the ratio of the rates of growth of squamous cell carcinoma and basal cell carcinoma, which is 3.6:1. Although purely inferential, this points to the basal type of cell as the progenitor of the basal cell carcinoma.

In conclusion one may say that the study of the present series of 182 specimens of basal cell carcinoma of the skin supports the concept of basal cell carcinoma as having multicentric points of origin in (*a*) the basal layer of the epidermis, (*b*) the sheaths of the hair follicles, (*c*) the pilar papillae, and (*d*) occasionally the sebaceous glands. A given tumor may arise from any one or from all of these structures. Definite evidence that basal cell carcinoma may originate also from the sweat glands was not found in the present series.

SUMMARY

The history of the development of knowledge of the basal cell carcinoma is reviewed, and the various theories of the histogenesis of this type of carcinoma are discussed and analyzed.

A study of 182 specimens of basal cell carcinoma is presented. The theory that basal cell carcinoma has a multicentric origin in the basal layer of the epidermis and/or in the pilosebaceous apparatus is supported. The evidence that it may arise also from the sudoriferous glands appears inconclusive.

16. Hoffman, J. G.: Arch. Path. **47**:37, 1949.

NONLIPID RETICULOENDOTHELIOSIS: LETTERER-SIWE DISEASE

Report of a Case

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ABOUT twenty-five years ago Letterer [1] reported splenohepatomegaly associated with anemia and a purpuric eruption which had occurred in an infant that died four days after being admitted to the hospital. Necropsy revealed marked proliferation of the reticuloendothelial cells, which were invading and replacing the normal structures of the liver, spleen, lymph nodes, bone marrow and skin. A similar case was reported by Siwe [2] in 1933, at which time he grouped his case with previously reported cases [3] as instances of what he believed to be a clinicopathologic entity. The criteria of this syndrome included a nonfamilial, nonhereditary disease of infants of unknown cause and fatal terminus, with an acute onset, hemorrhagic tendencies, secondary progressive anemia, lymphadenopathy, splenomegaly, hepatomegaly and localized tumors of bone. The morphologic changes consisted of generalized hyperplasia of the reticuloendothelial system with characteristic large mononuclear cells which were not lipid storing. Abt and Denenholz [4] chose the title "Letterer-Siwe's Disease" to cover this disease process.

Because the number of cases up to last year (1948) which met the original established criteria for this disease did not exceed 24,[5] and because of the present lack of uniformity in the correlation of the so-called reticuloendothelioses, it was deemed justifiable to report another case which falls in this rare category and which might aid in the future clarification and classification of the cases of disease of the reticuloendothelial system.

REPORT OF CASE

An 11 month old white girl was admitted to Temple University Hospital in a serious condition. She was born, Jan. 18, 1948, as a full term, spontaneous vertex delivery with a labor of seventeen hours. The birth weight was 8 pounds 4 ounces

From the Department of Pathology, Temple University School of Medicine.

1. Letterer, E.: Frankfurt. Ztschr. f. Path. **30**:377, 1924.
2. Siwe, S.: Ztschr. f. Kinderh. **55**:212, 1933.
3. (*a*) Letterer.[1] (*b*) Akiba, R.: Virchows Arch. f. path. Anat. **260**:262, 1926. (*c*) Guizetti, H. U.: ibid. **282**:194, 1931.
4. Abt, A. F., and Denenholz, E. J.: Am. J. Dis. Child. **51**:499, 1936.
5. Schafer, E. L.: Am. J. Path. **25**:49, 1949.

(3.7 Kg.). The mother, the father and a brother, 3 years of age, were in normal health. The child was immunized for diphtheria and pertussis in September and October 1948 and for smallpox in November 1948. Her development was considered normal, and she had no previous illnesses or hospitalizations.

The infant was in apparently good health until about three weeks prior to admission, at which time there was an onset of a "throat infection," accompanied by a slight cough and a rectal temperature of 104 F. Treatment consisted of oral administration of sulfonamides, with abatement of symptoms in three days.

Nothing unusual was then observed until ten days prior to admission, at which time it was noted that the child became listless. A slight nonproductive cough developed, accompanied by a low grade fever. Her temperature returned to normal after two days. This was followed by mild postprandial vomiting, which also subsided in two days. On December 13, six days prior to admission, an eruption was observed in the vulvar area which was diagnosed as a diaper rash. This "rash" gradually spread to involve the trunk, the face and all the extremities. In addition, vomiting again became manifest, and on the day prior to admission the child regurgitated all of her feedings. A few hours before she was brought to the hospital obvious dyspnea became apparent. Her condition became grave, and she was admitted to the hospital for treatment on December 19.

Examination revealed a well developed, well nourished white girl who was obviously seriously ill. The rectal temperature was 95 F. A marked pallor and multiple petechiae were noted over the face, scalp, trunk, upper arms, labia and about the anus. A few shotty left posterior cervical nodes were palpable. A blowing systolic murmur was audible at the left second interspace. The liver was palpable 3 cm. below the costal cage on the right, and the spleen was palpable 4 cm. below the rib cage on the left. Both were firm and smooth. The extremities were flaccid, and there was mild pitting edema of the legs.

An intern who made a blood count on the evening of her admission reported 7.5 Gm. of hemoglobin, 1,250,000 erythrocytes and 41,100 leukocytes with many "blast" forms. On the basis of the clinical and laboratory findings a tentative diagnosis of acute leukemia was made, and treatment was begun immediately. This included transfusion of whole blood (500 cc.), administration of penicillin, aminopterin (4-aminopteroylglutamic acid) (1 mg.) and crude liver extract, and supportive oxygen therapy. The following morning the hematologic studies were repeated, and a biopsy of tibial marrow was made. The peripheral blood revealed: 7.2 Gm. of hemoglobin; 2,540,000 erythrocytes; 5,900 leukocytes, with neutrophilic myelocytes 73 per cent, lymphocytes 23 per cent and monocytes 4 per cent; 5,100 thrombocytes and 63 nucleated erythrocytes per hundred leukocytes. (The latter were probably misinterpreted in the original examination made by the intern.) Slight bleeding from small fissures and ulceration of the lips and mouth occurred in addition to minimal hemorrhages of the nose and the vagina. The stools were tarry. A low grade fever made its appearance and persisted for the remainder of the patient's illness. The biopsy of the marrow revealed: neutrophilic, segmented cells of the granulocytic series, 8.3 per cent; eosinophilic cells of this series, 0.7 per cent; progranulocytes, 3.3 per cent; mitotic figures, 1.0 per cent; lymphocytes, 6.3 per cent; nucleated erythrocytes (rubricytes), 66.0 per cent; prorubricytes, 10.3 per cent; rubriblasts, 4.0 per cent; erythroid-myeloid ratio, 80.3:19.7 or 1.02. Because of the findings and the enormous increase in nucleated red cells in the peripheral blood, the impression was that of an "erythroblastic hyperplasia (anemia) associated with hemorrhage, leukopenia and thrombopenia."

An additional transfusion of 500 cc. of whole blood was given on December 23. Examination of the eyegrounds revealed only extreme generalized pallor. The

following day a test of the epinephrine response[6] was made, which showed a slight rise in the circulating leukocytes. It was felt at this time that the picture fitted "Doan's splenic panhematopenia syndrome."[6] However, because of the increasing gravity of the child's condition and because of some response as measured by the epinephrine test, the spleen was removed on December 24, with the patient under open drop ether anesthesia. Three hundred cubic centimeters of whole blood was given during the operation.

The removed spleen measured 10 by 7 by 3.5 cm. and weighed 120 Gm. (normal, 25 Gm.). The external surface was not remarkable. The parenchyma was firm; no follicles were demonstrable, and the cut surfaces showed multiple dark areas suggesting hemorrhage. At one pole there were several small irregular white areas which had an appearance not unlike tubercles. Microscopic examination showed recent areas of hemorrhage and necrosis. In other fields multiple irregular areas of infarction were present. The sinusoids were greatly distended, and in many there were large young cells resembling histiocytes. The follicular pattern was completely effaced by the aforementioned changes, and one of the most interesting features noted was multiple areas of hemopoiesis, which was presumed to represent myeloid metaplasia. The changes were considered so nonspecific that a definitive diagnosis could not be made.

The postoperative course continued to be relatively good, and it was felt that the general condition of the patient was better than prior to splenectomy. On December 28 the coagulation time was reported as 2 minutes 50 seconds and the bleeding time as 1 minute. On the following day the child's temperature was 103 F., the highest recorded since her admission. The cause of the febrile course continued to remain obscure. Laboratory studies now revealed a hemoglobin level of 9.7 Gm. with erythrocytes 3,410,000, thrombocytes 13,600 and plasma carbon dioxide 51.5 volumes per cent. No icterus was noted, and repeated blood cultures continued to be negative.

On December 29 a biopsy of tibial marrow yielded a differential count that was considered approximately normal but (1) the nucleated cells were scarce and (2) the granules in the neutrophilic myelocytes were pseudobasophilic ("toxic"). It was considered that the clinical course, as well as the blood and the marrow, except the neutropenia, were improving, and continuation of supportive therapy was advised. Additional laboratory studies showed the blood urea nitrogen to be 11 mg., the serum proteins 4.5 Gm. (albumin-globulin ratio 1:4) and the blood sugar 65 mg. per hundred cubic centimeters. A roentgenologic survey of the skeleton revealed no roentgen evidence of any abnormality in density, texture or contour of the various bony structures.

The febrile course continued, but no new petechiae were noted, although the lesions over the dorsum of the body were becoming confluent. On January 2 another 250 cc. of whole blood was given because of decline of the erythrocytes to 2,500,000 and of the hemoglobin to 8.2 Gm. The healing of the splenectomy incision continued to be slow. On January 3 a roentgenogram of the chest revealed some density supra-adjacent to the right hilus, which was interpreted as pneumonitis or pneumonia confined to the apical segment of the lower lobe of the right lung. The hematologic picture revealed only a slow decline, and the child appeared to be showing gradual clinical improvement.

This transient period of clinical improvement did not continue. On January 13 a new crop of petechial hemorrhages was observed over both temporal regions and over the upper part of the trunk. The following day tibial marrow and

6. Doan, C. A., and Wright, C. S.: Blood **1**:10, 1946.

spinal fluid were removed for routine examinations as well as for special studies for Histoplasma and other fungi. The spinal fluid was reported as containing 18 mg. of protein and 122 mg. of sugar per hundred cubic centimeters, with no bacterial growth on aerobic, anaerobic and carbon dioxide cultures. The marrow films could not be interpreted. Many large, degenerated cells with vacuolated cytoplasm and fragmented nuclei were observed. These gave the appearance of "overheated," degenerated cells, conditions due to improper preparation. Insufficient cells were recognizable to make a differential count. "Gaucher's cells" were considered, but none sufficiently characteristic were visualized. Another aspiration of marrow was requested.

On January 16 the erythrocyte count was 3,100,000 and the hemoglobin value was 9.6 Gm.; the leukocyte count was 3,800, with neutrophilic myelocytes 29 per cent, lymphocytes 68 per cent and monocytes 3 per cent. No thrombocytes were seen, and 27 nucleated erythrocytes per hundred leukocytes were noted. A transfusion of whole blood, 170 cc., was given, and another 170 cc. was given on the following day. Administration of folic acid, a vitamin K analogue (synkayvite® [tetrasodium, 2-methyl-1, 4-naphthohydroquinone, diphosphoric acid ester]), ascorbic acid, a multivitamin preparation, penicillin, desoxycorticosterone acetate and supplemental parenteral protein hydrolysates (amigen®) was continued. Fecal cultures were negative for non-lactose-fermenting organisms, and agglutination tests for typhoid and paratyphoid were negative. New petechiae continued to appear and now covered almost all of the skin surfaces, being most marked on the head and the trunk. The general condition of the patient continued to be unsatisfactory.

On January 20 the tibial marrow revealed very few nucleated red cells and a differential count similar to the differential count of the peripheral blood of the same date. The question of aplastic marrow was considered. Again many large cells with foamy cytoplasm were observed, and the strong possibility of a lipid storage disease was proposed.

On January 25 another 100 cc. of whole blood was given by transfusion because of a regression in the blood picture. New petechiae continued to appear; the skin became waxy and pallid, and the appetite poor. At this time the diagnosis of Letterer-Siwe disease was considered most likely. Another roentgenologic skeletal survey was made, which revealed some demineralization as contrasted with the previous examination (four weeks prior to this). The demineralization was considered nonspecific and was best seen in the metaphysial areas of several of the long bones. Another 250 cc. of blood was given by transfusion on January 27 because of a hemoglobin value of 4.9 Gm. and an erythrocyte count of 1,650,000. Only slight clinical improvement followed. Smears and cultures of the spinal fluid and tibial marrow were reported negative for Histoplasma and other fungi. The petechiae became more confluent; the child became progressively paler and weaker; the respiratory rate increased, and on February 2 the patient died, fifty-four days after the onset of symptoms.

Autopsy.—The subject was a thin white girl who weighed 15 pounds (6.8 Kg.). Numerous dark and recent petechiae were present over the entire body, most marked over both lower extremities and over both forearms, at which sites they were almost confluent (fig. 1). There was slight pitting edema of the vulva and both lower extremities. Petechiae were noted in the conjunctivas, and the gingivae had recent small hemorrhagic ulcerations. The oral mucous membranes were pallid, and petechiae were observed on the hard and soft palates. A granulating surgical incision was present in the left upper quadrant of the abdomen. No peripheral lymphadenopathy or icterus was present.

The serosal surfaces of the thoracic viscera were of a light gray–yellow pallor. The pericardium contained approximately 10 cc. of clear, light amber fluid. Fibrinous adhesions were present between the various serosal surfaces in the left upper region of the abdominal cavity. The serosal surfaces of the large bowel

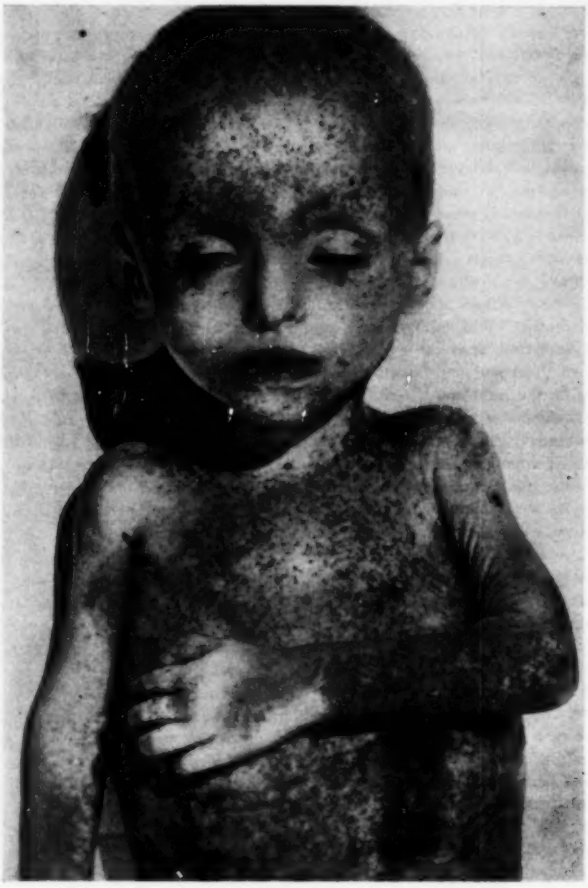

Fig. 1.—Patient showing generalized hemorrhagic manifestations and a granulating abdominal surgical wound. Note the confluence of lesions on the forearm.

showed numerous diffuse dusky darkened areas, some of which were confluent, grossly suggesting submucosal hemorrhages.

The heart weighed 39 Gm. (normal, 44 Gm.) and was grossly normal except for a definite pallor of the myocardium. The right lung weighed 77 Gm.; the

left, 67 Gm. (normal, 64 to 57 Gm.). The pleural surfaces were finely lobulated and presented a smooth, very pale yellow-gray appearance. All lobes were firm and elastic on palpation, and cut sections again presented rather homogeneous, pale yellow-gray surfaces.

The adrenal glands showed a definite pallor. The right kidney weighed 27 Gm.; the left, 42 Gm. (normal, 36 Gm.). The cortical surfaces and the cut sections were not unusual except for a firm consistency and a pallid appearance.

The liver was grossly enlarged and weighed 400 Gm. (normal, 288 Gm.). The organ was firm, and cut sections revealed a pale tawny parenchyma.

The entire large bowel contained a considerable amount of tarry fecal material. The submucosa of the large intestine presented numerous patchy, circumscribed, at times confluent, areas of purple discoloration which grossly suggested submucosal hemorrhage. The major finding in the abdominal cavity was the marked enlargement of the periaortic and mesenteric lymph nodes. The nodes measured up to 2 cm. in diameter and for the most part were matted and of a semirubbery consistency. The cut surfaces were pale yellow-brown, and interspersed were numerous small and confluent areas of recent and old hemorrhage.

The brain weighed 750 Gm. (normal, 925 Gm.). Over both cortical surfaces several small punctate areas of old hemorrhage were noted. After fixation and coronal sectioning of the brain, the described punctate areas of hemorrhage appeared to be confined to the cortical aspects of the hemispheres, the deeper structures being grossly uninvolved.

The marrow of the ribs, long bones and vertebral bodies was light tan and of homogeneous appearance. Except for distinct pallor, gross observations of the other structures and viscera revealed nothing remarkable.

Microscopic Observations.—Microscopic examination of the brain revealed small irregular areas of recent and old hemorrhage in the cortical and subcortical regions. These measured up to 2 mm. in diameter and were confined to the peripheral portions of the cerebral hemispheres; the deeper structures, the cerebellum and the brain stem remained uninvolved.

All the lymph nodes examined presented an almost identical picture. The normal structure was effaced by the presence of large numbers of atypical mononuclear cells (fig. 2). The nodes were traversed by long stringy bands of collagenous tissue in which a few intermingling fibroblasts could be observed. Germinal centers could not be recognized, and the normal lymphoid elements were almost completely replaced by accumulations of loosely arranged atypical mononuclear cells. The predominant cells were of irregular outline with acidophilic cytoplasm. The nuclei were oval, lobulated, irregular or indented and eccentrically located. The intensity of nuclear staining varied, the smaller nuclei staining darkly, whereas the larger nuclei were vesicular and stained lighter. The cytoplasm was eosinophilic and finely granular and in many cells was finely vacuolated. Multinucleated cells were rare. Some of the cells showed phagocytosis of dark brown pigment granules and contained small vacuoles. These cells were most prominent in the peripheral sinuses. Rare small collections of large cells with pale, eccentrically placed nuclei and foamy cytoplasm were noted in perivascular locations in the central portions of a few of the nodes examined. Small areas of recent and old hemorrhage were noted in some of the nodes, and in many there were small foci of necrosis. These granulomatous-like areas were conspicuous because of the lack of neutrophilic myelocytic or lymphocytic response at their periphery. Sections stained with scarlet red showed that the cytoplasm of some of the large foam cells in the perivascular sites contained small amounts of lipiod material. Osmic acid did not stain these cells. Reticulum stains revealed marked proliferation of reticulum throughout all of the nodes. Masson's stain was not

particularly helpful but again demonstrated the prominent stringy bands of connective tissue. Frozen sections examined under crossed Nicol prisms did not show any doubly refractile bodies.

The thymus gland could not be recognized as such because the normal tissue had been almost completely replaced by a loose collagenous network which contained small numbers of fibroblasts. Small areas of recent and old hemorrhage with focal necrosis and scattered macrophages containing pigment granules were noted throughout the parenchyma. A diffuse sprinkling of small cells with darkly staining oval, irregular or elongated nuclei and sparse cytoplasm was seen, most evident near sites of capillary proliferation. Numerous atypical cells were again in abundance, many with pale granular cytoplasm and with most of their nuclei pale staining and lobular or greatly indented. Scattered multinucleated giant

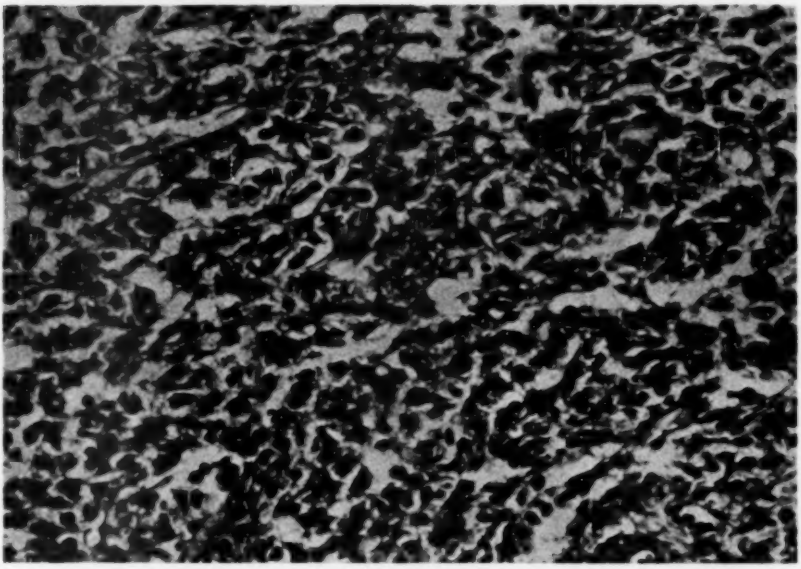

Fig. 2.—Lymph node showing diffuse involvement. The normal structure has been replaced by atypical mononuclear cells. Hematoxylin and eosin; high power magnification.

cells were noted (fig. 3). Only an occasional large cell with foamy cytoplasm was encountered. Frozen sections did not stain with scarlet red or with osmic acid, and tissues examined with polarized light revealed no abnormality.

Several of the periportal areas of the liver were conspicuous because of small aggregates of atypical mononuclear cells. Occasional small collections were noted adjacent to some of the bile ducts, while at other sites, not related to any of the periportal areas, similar small collections were present. The Kupffer cells were prominent, and many were heavily laden with dark brown pigment. The sinusoids were moderately dilated and congested, and in a few areas the sinusoids were very prominent and contained large polyhedral cells which appeared to be liberated and degenerating liver cells.

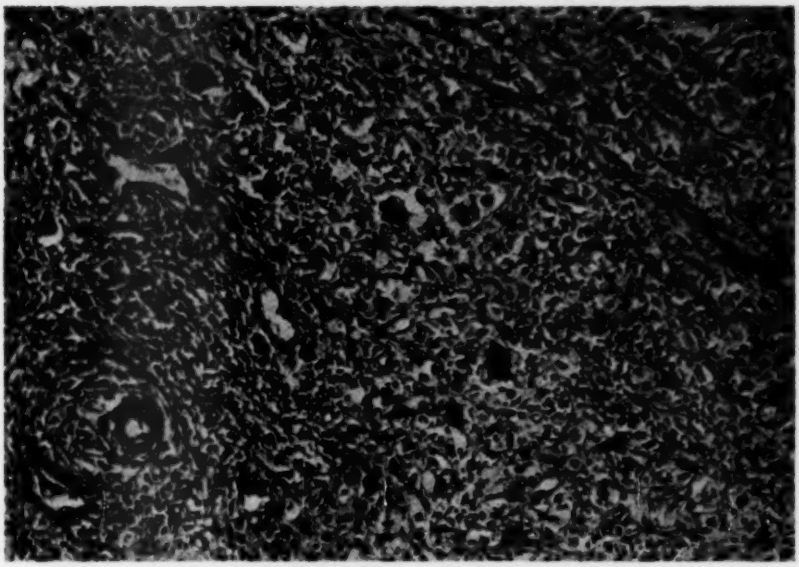

Fig. 3.—Thymus showing numerous giant cells and collections of atypical mononuclear cells that completely alter the normal pattern. Hematoxylin and eosin; low power magnification.

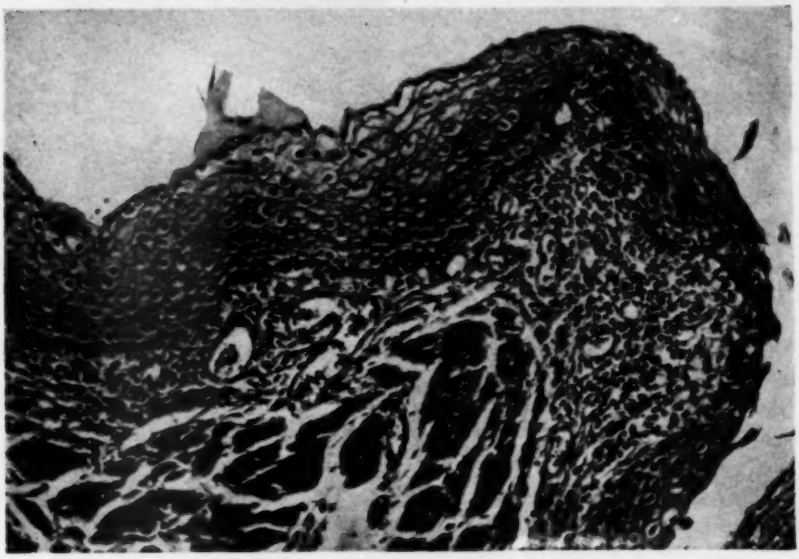

Fig. 4.—Cutaneous lesion showing collections of mononuclear reticuloendothelial cells in the corium. Hematoxylin and eosin; microtessar.

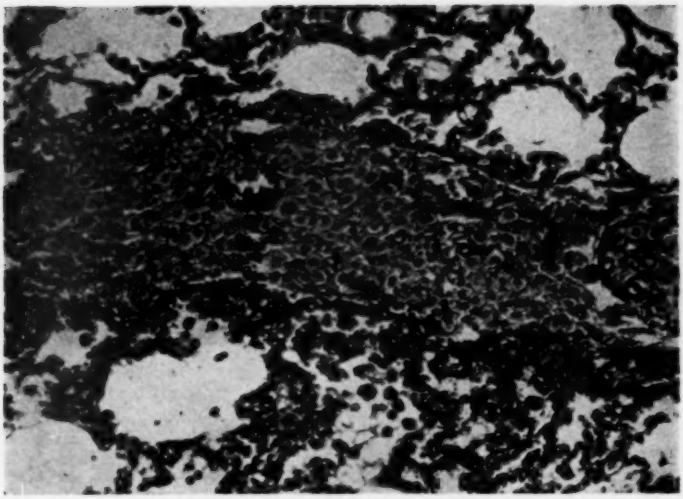

Fig. 5.—Lung with traversing band of large atypical cells. Pleural surfaces presented a similar appearance. Hematoxylin and eosin; high power magnification.

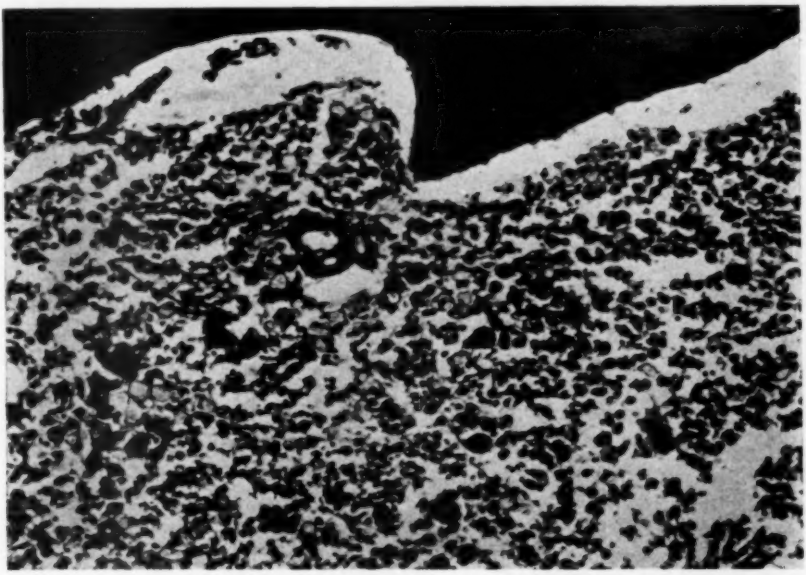

Fig. 6.—Marrow with normal elements almost completely replaced by diffuse collections of mononuclear reticuloendothelial cells. Hematoxylin and eosin; high power magnification.

The epithelium of the skin showed patchy areas of thinning with collections of similar atypical mononuclear cells and lymphocytes in abundance in the corium (fig. 4). Small areas of recent and old hemorrhage were also noted.

The submucosa of the large intestine revealed small areas of hemorrhage and interglandular collections of atypical mononuclear cells. The normal lymphoid follicles were almost completely replaced by similar cells and occasional larger macrophages. In some areas the overlying mucosa was thinned and ulcerated.

The pleura was thickened by loose collections of large, atypical mononuclear cells with pale, granular cytoplasm, and the interlobular septums of the lung were conspicuous and widened by bands and sheets of similar cells (fig. 5). The perivascular and peribronchial regions presented focal accumulations of similar cells. A few large, pigment-laden macrophages were present in some of the alveolar spaces. Fat stains were negative, and examination with Nicol prisms revealed no doubly refractile bodies.

Sections from the sternum, vertebral bodies and long bones revealed essentially similar changes. There was almost complete destruction of the normal hemopoietic cellular elements by similar atypical mononuclear cells (fig. 6). Occasional large macrophages with vacuolated cytoplasm were present. Giemsa stains demonstrated the decrease in normal cellular components more prominently than hematoxylin and eosin.

COMMENT

The clinical course and the anatomic findings in this case leave little doubt that it represents a disease of the reticuloendothelial system known as Letterer-Siwe disease.

Three weeks prior to the onset of the acute phase of the disease the patient had a "throat infection" which rapidly responded to sulfonamide therapy. Whether this illness was related to the development of the subsequent disease is not known, and no definite infectious agent can be directly implicated.

The patient was an infant, and the onset was acute and characterized by hemorrhagic phenomena, fever, splenomegaly and hepatomegaly. There was no familial history. The course of the disease was rapid and accompanied by severe anemia. These may be regarded as typical clinical findings. Only a few small posterior cervical nodes were palpable early in the disease; however, marked mesenteric lymphadenopathy was present at the termination of the illness.

Acute leukemia was suspected at the time of admission on the basis of the clinical findings and a peripheral blood smear which was interpreted to show numerous "blast forms." In addition to other immediate therapy a small amount (1 mg.) of aminopterin was given. However, the original diagnosis was not verified a few hours later when a competent hematologist viewed the peripheral blood and marrow slides and noted that the previously reported "blast forms" were in reality nucleated erythrocytes, which were present in great numbers. It is known that aminopterin exerts suppressive effects on the lymphoid and myeloid elements.[7] Because the total amount of this agent given was so small

7. Farber, S.: Blood **4**:160, 1949.

and because subsequent therapy probably nullified any obvious effects, it was felt that this drug did not in any way materially alter the clinical course and the gross and microscopic alterations in this case.

The cause of the fever remained obscure until the disease was well advanced. Pathologic examination of the removed spleen revealed large histiocytes in some of the dilated sinusoids, but the remainder of the organ was so completely effaced by areas of hemorrhage, infarction and hemopoiesis that the import of these cellular collections was not fully realized at that time.

The original skeletal survey showed nothing of importance, and a subsequent one, twenty-five days later, revealed only minor nonspecific demineralizations of the metaphysial areas of several of the long bones.

The peripheral blood revealed a rather constant progressive severe anemia with numerous nucleated red cells. The leukocyte count was constantly low, with a relative lymphocytosis, accompanied by marked lowering of the thrombocytic level. The marrow was studied on four occasions because of the lack of a definitive diagnosis. The first two studies were not diagnostic, the third revealed large cells which were interpreted as an artefact, but on the fourth examination these cells were again in evidence and the likelihood of a lipid storage type of disease was strongly suspected.

Bacteriologic studies of blood, urine, feces, marrow and spinal fluid, as well as other studies for fungi and histoplasma, gave constantly negative results. Intensive therapy did not alter the progressive course of the disease.

The reticuloendothelial apparatus has a wide distribution and serves a diversity of functions. It is primarily composed of three main types of cells: monocytes, histiocytes and the reticuloendothelial cells, proper. The latter may be cells attached to the reticulum of the organs of hemopoiesis or endothelial cells that line the sinusoids of the liver, lymph nodes, marrow and spleen. The main function of this collection of cells is varied but includes phagocytosis, the formation of blood cells, the production of antibodies and also storage. Many enigmas and heterologous disease processes have been attributed to various alterations of this system, and many have been grouped under the all-inclusive term "reticuloendotheliosis." These have included some infectious diseases, such as tuberculosis, malaria and typhoid; the so-called lipid storage diseases, such as Gaucher's disease (kerasin), Neimann-Pick disease (phosphatide) and Schüller-Christian disease (cholesterol); xanthomatosis and diabetic lipemia; certain leukemias, for instance, monocytic leukemia; neoplastic diseases, such as reticulum cell sarcoma; Hodgkin's disease, and, finally, Letterer-Siwe disease.

The original criteria for Letterer-Siwe disease[2] (also called nonlipoid reticuloendotheliosis and aleukemic reticulosis) included a pro-

liferation of the cells of the reticuloendothelial system due to a noninfectious cause, thus tending to separate it from the infectious group. Some have adhered to the original premise.[8] Other writers,[9] in reviewing their own cases as well as some of those of others that had been previously reported, have expressed the belief that infection plays either a primary or a secondary causative role. Wallgren [10] challenged the belief that the infectious and the noninfectious reticuloendothelioses represent separate entities.

The original criteria [2] also included the observation that the macrophages were nonlipid storing. In 1940 Glanzman [11] reported a case in which lipoid material was seen in some of the granulomatous lesions, an observation that led him to believe that the disease was closely related to Schüller-Christian disease. Others [12] also have postulated or suggested that overlapping occurred between the two diseases. Several cases [13] in which the disease processes represent intermediate, mixed or borderline forms strongly support this view.

Green and Farber [14] made an attempt to correlate Letterer-Siwe disease with other diseases of the reticuloendothelial system, namely, Schüller-Christian disease and eosinophilic granuloma of bone because of histologic similarities noted in various stages of these disease proc-

8. (*a*) Akiba.[2b] (*b*) Prodvinec, E., and Terplan, K.: Arch. f. Kinderh. **93**:40, 1931; cited by Abt and Denenholz.[4] (*c*) Siwe.[2] (*d*) Foot, N. C., and Olcott, C. T.: Am. J. Path. **10**:81, 1934. (*e*) Abt and Denenholz.[4] (*f*) Schafer.[5]

9. (*a*) Letterer.[1] (*b*) Schultz, A.; Wermbter, F., and Pufl, H.: Virchows Arch. f. path. Anat. **252**:519, 1924; cited by Schafer.[5] (*c*) Krahn, H.: Deutsches Arch. f. klin. Med. **152**:179, 1926; cited by Wallgren.[10] (*d*) Akiba.[9b] (*e*) Sherman, I.: Arch. Path. **7**:78, 1929. (*f*) Guizetti.[9c] (*g*) Prodvinec and Terplan.[8b] (*h*) Gittens, R.: Arch. Dis. Childhood **8**:367, 1933. (*i*) Uher, V.: Virchows Arch. f. path. Anat. **289**:504, 1933. (*j*) Klostermeyer, W.: Beitr. z. path. Anat. u. z. allg. Path. **93**:1, 1934; cited by Wallgren.[10] (*k*) Foot and Olcott.[8d] (*l*) Mallory, T. B.: New England J. Med. **227**:955, 1942. (*m*) Jaffe, H. L., and Lichtenstein, L.: Arch. Path. **37**:99, 1944.

10. Wallgren, A.: Am. J. Dis. Child. **60**:471, 1940.

11. Glanzman, E.: Ann. pædiat. **155**:1, 1940.

12. (*a*) Glanzman.[11] (*b*) Wallgren.[10] (*c*) Freud, P.; Grossman, L., and Dragutsky, D.: Am. J. Dis. Child. **62**:776, 1941. (*d*) Gross, P., and Jacox, H. W.: Am. J. M. Sc. **203**:673, 1942.

13. (*a*) Schultz and others.[9b] (*b*) Erber, L. J.: Virchows Arch. f. path. Anat. **282**:621, 1931. (*c*) Merritt, K. K., and Paige, B. H.: Am. J. Dis. Child. **46**:1368, 1933. (*d*) Grady, H. G., and Stewart, H. L.: Arch. Path. **18**:699, 1934. (*e*) Galeotti Flori, A., and Parenti, G. C.: Riv. di clin. pediat. **35**:193, 1937; cited by Freund and Ripps.[13h] (*f*) Lane, C. W., and Smith, M. G.: Arch. Dermat. & Syph. **39**:617, 1939. (*g*) Sweitzer, S. E.; Winer, L. H., and Cummings, H. A.: ibid. **40**:192, 1939. (*h*) Freund, M., and Ripps, M. L.: Am. J. Dis. Child. **61**:759, 1941.

14. Green, W. T., and Farber, S.: J. Bone & Joint Surg. **24**:499, 1942.

esses. Jaffe and Lichtenstein [15] and others [16] have believed that they represent varying gradations of severity of the same basic process: an acute and fatal form, in which the reticuloendothelial cells show little or no lipid deposition (Letterer-Siwe disease); a chronic form, with a protracted clinical course, characterized by typical foam cells containing cholesterol (Schüller-Christian disease), and, finally, a benign form of the same basic process in which recovery is apt to occur (eosinophilic granuloma). It is true that all have some clinical, roentgenographic and morphologic features which suggest that they may represent different phases of the same basic disorder.[16]

In the literature it is at once apparent that there are numerous opinions as to the proper classification, the cause and the true nature of this unusual proliferation of the reticuloendothelial system. One who would take a fixed position on this yet unsettled condition would indeed be intrepid. The reader is referred to a recent excellent review by Schafer [8] for a more complete treatment of this subject.

SUMMARY

A case of Letterer-Siwe disease (nonlipid reticuloendotheliosis) is presented. It is believed that in this case the disease was initiated by an infectious process that occurred three weeks prior to the onset of the acute symptoms.

Similarities noted in roentgenographic, morphologic and some clinical features strongly suggest that Letterer-Siwe disease, Schüller-Christian disease and eosinophilic granuloma represent similar types of a fundamental basic disorder of the reticuloendothelial system.

15. Jaffe, H. L., and Lichtenstein, L.: Arch. Path. **37**:99, 1944.

16. (*a*) Farber, S.: Am. J. Path. **17**:625, 1941. (*b*) Mallory.[9l] (*c*) Gross and Jacox.[12d] (*d*) Curtis, A. C., and Crowley, E. P.: Arch. Dermat. & Syph. **55**:810, 1947. (*e*) Dundon, C. C.; Williams, H. A., and Laipply, T. C.: Radiology **47**:433, 1946. (*f*) Guizetti[3c]; cited by Gross and Jacox.[12d] (*g*) Straus, B.: Am. J. Med. **5**:245, 1948.

THE SYNDROMES OF THE CEREBRAL ARTERIES

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MINNEAPOLIS

THE STUDY of the syndromes resulting from occlusions of the various cerebral arteries is frequently neglected because it does not have immediate clinical application. This disregard also may be attributed to the diversity of opinions and the inadequate consideration given the subject in the standard references. Yet exact information on this subject is critical for cerebral localization and yields a practical framework for experimental and surgical procedures as well as having direct prognostic and therapeutic significance.

A number of methods have been employed in the investigation of the cerebral arteries. Their fields of distribution have been determined by dissection, injection of dyes, and comparative studies of species lower in the phylogenetic series. Correlations of the clinical and pathologic observations have produced descriptions of typical syndromes. However, these are often confusing unless cognizance is given to certain factors responsible for variations in the clinical picture. These include: anomalies of the vessels; collateral circulation; cerebral dominance; ability of intact parts to undertake new functions; effect of diaschisis; variations in the site of occlusion of any one vessel; the presence of more than one occlusion, cerebral arteriosclerosis or other pathologic processes; variations in the size of the areas of cortical representation; overlap of the fields of distribution of the various vessels.

In the present work an effort has been made to review and clarify the available literature and include the anatomic and clinical aspects in outline form. The outline form was chosen as being most suitable not only to stress the cardinal features but also to include the minor details which the reader might wish for reference. The sections on the fields of distribution of the various vessels are derived mainly from the excellent work of Beevor,[1] that on the anterior cerebral artery from Critchley[2] and that on the anterior choroidal artery from Abbie.[3]

From the Division of Neurology, University of Minnesota Medical School.

1. Beevor, C. E.: Brain **30**:403, 1907.
2. Critchley, M.: Brain **53**:120, 1930.
3. Abbie, A. A.: Brain **56**:233, 1933.

THE INTERNAL CAROTID ARTERY

Course.—The internal carotid artery arises from the common carotid artery at the level of the upper border of the thyroid cartilage. It passes through the carotid canal in the petrous portion of the temporal bone and through the foramen lacerum to reach the cranial cavity. It continues to the anterior clinoid process, where it pierces the dura mater and attains the base of the brain at the beginning of the fissure of Sylvius. Here it rests on the anterior perforated substance and lies between the optic and the oculomotor nerves.

Branches.—1. The ophthalmic artery is the only large branch given off by the internal carotid artery before it reaches the brain. The branch passes through the optic foramen and sends further branches to the ocular muscles, the retina and the lacrimal apparatus.

2. Terminal branches. These include the anterior cerebral artery, the middle cerebral artery, the posterior communicating artery and the anterior choroidal artery.

Clinical Significance.—Occlusion of the internal carotid artery may cause no or minimal clinical signs if the circle of Willis is competent (Brock [4]). However, rapid closure of the vessel may result in convulsions and death in some patients. Contralateral hemiplegia and hemianesthesia plus complete aphasia (if the closure is in the major hemisphere) may occur. Involvement of the ophthalmic artery causes ipsilateral blindness.[4] The lodging of a thrombus or an embolus in the internal carotid artery at the origin of the ophthalmic artery results in contralateral hemiplega with ipsilateral primary optic atrophy (Alpers [5]).

THE ANTERIOR CEREBRAL ARTERY

Course.—From its origin, the anterior cerebral artery first courses anteriorly and medially along the anterior perforated substance, then between the olfactory tubercles and the optic nerves to lie at the margin of the mesial and orbital surfaces of the hemisphere. Here it connects with the corresponding vessel of the opposite side via the anterior communicating artery. It then turns up and forward over the genu of the corpus callosum and courses along the epicallosal sulcus. It ends by going up obliquely along the parietal lobe to the square or quadrate lobe or to the parieto-occipital fissure.

Field of Distribution.—1. The entire mesial surface of the frontal and parietal lobes to a depth of 2.5 cm.

4. Brock, S. J.: Basis of Clinical Neurology, Baltimore, William Wood & Company, 1937.

5. Alpers, B. J.: Vascular Diseases of the Brain in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1944, vol. 10.

2. The orbital surface of the frontal lobe from the midline to the external limit of the internal orbital convolution.

3. The genu and anterior four fifths of the corpus callosum.

4. The septum pellucidum, upper parts of the anterior pillars of the fornix, and the medial parts of the anterior commissure.

5. The inferior aspect of the anterior portion of the head of the caudate nucleus, of the anterior part of the two outer segments of the lenticular nucleus, and of the anterior one half of the forelimb of the internal capsule.

Branches.—1. Basal branches: There are three or four branches which pierce the anterior perforated substance to supply the head of the caudate nucleus. One of these, the recurrent artery of Heubner, supplies the following structures:

(*a*) Olfactory peduncle.

(*b*) The anterior part of the caudate nucleus.

(*c*) The anterior third of the putamen.

(*d*) Tip of the outer segment of the globus pallidus.

(*e*) The anterior limb of the internal capsule.

(*f*) Rubenstein [6] included the external capsule and the genu of the internal capsule in the distribution of the recurrent artery of Heubner.

2. Anterior communicating artery. This has no branches.

3. Branches from the convexity:

(*a*) The prefrontal branch is the largest and goes to the medial aspect of the frontal lobe and supplies Brodmann's area 11.

(*b*) The frontopolaris branch supplies the superior part of the superior frontal gyrus. (Brodmann's area 10.)

(*c*) The anterior internal frontal branch arises at the level of the genu and supplies the mesial part of area 9.

(*d*) The middle internal frontal branch ends in the upper or posterior end of the superior frontal gyrus (area 8).

(*e*) The posterior internal frontal branch ends in the uppermost limit of the precentral fissure (area 6).

(*f*) The paracentral artery ends in the paracentral lobule.

(*g*) Superior parietal branches are also occasionally present. These end in the postcentral cortex and superior parietal convolutions.

(*h*) The precuneal branch supplies the mesial part of area 7.

6. Rubenstein, H. S.: Arch. Neurol. & Psychiat. **52**:526, 1944.

(*i*) Occasionally the anterior cerebral artery ends as the parieto-occipital branch which ends in the parieto-occipital fissure.

4. Branches from the concavity consist of a number of short twigs to the genu and body of the corpus callosum. Some of these penetrate and supply the septum pellucidum, part of the anterior commissure and the anterior pillars of the fornix.

Clinical Significance.—The syndromes vary according to the sites of the artery at which occlusions occur.

1. Total occlusion of the anterior cerebral artery (including Heubner's artery).

(*a*) Contralateral severe hemiplegia due to involvement of the anterior part of the internal capsule and the paracentral lobule. Involvement of the internal capsule causes paralysis of the contralateral half of the tongue and lower part of the face, and the arm, especially of the proximal part of the arm. Damage to the paracentral lobule results in paralysis of the leg, especially in its distal part.

(*b*) Mild sensory loss over the paralyzed lower extremity due to involvement of the mesial part of the postcentral gyrus.

(*c*) If the hemiplegia is right-sided, left-sided ideomotor apraxia appears. Critchley [2] expressed the belief that this is due to the involvement of the corpus callosum. If the right anterior cerebral artery is affected, the left-sided apraxia will be masked by the severe motor paralysis of the extremity and the right extremities will be normal in this case, according to Critchley. Nielson [7] attributed ideokinetic apraxia to lesions of the corpus callosum as well as to lesions of the major supramarginal gyrus (which is supplied by a branch of the middle cerebral artery).

(*d*) Mental changes—retardation, confusion, disorientation, and occasionally dementia, witzelsucht and coma. Incontinence of urine and feces may occur. All these findings are attributed to callosal and frontal lobe involvement. The incontinence may be due to involvement of the paracentral lobule or related to the mental changes.

(*e*) Aphasia occurs if the lesion is in the major hemisphere. It is of the motor type and usually temporary and mild.

2. Occlusion of the anterior cerebral artery after emergence of the recurrent artery of Heubner and the anterior communicating artery.

7. Nielson, J. M.: Agnosia, Apraxia, Aphasia, New York, Paul B. Hoeber, Inc., 1946.

(*a*) Hemiplegia with crural predominance due to direct involvement of the leg area of the paracentral lobule. This hemiplegia is often of the flaccid type,[4] which may indicate that the lesion is limited to area 4 and spares area 6.

(*b*) Indefinite sensory impairment in the affected part, especially the leg, due to involvement of the postcentral gyrus.

(*c*) Left-sided apraxia regardless of which hemisphere is affected.

(*d*) Mental changes—retardation, confusion, occasionally coma.

(*e*) Aphasia if the lesion is on the major side. This is usually transient and associated with dysarthria. In a case in Critchley's [2] series there were also echolalia and palilalia.

(*f*) Forced grasping and groping movements may be noted in the hemiplegic upper extremity.

3. Occlusion of the individual branches of the anterior cerebral artery.

(*a*) Occlusion of Heubner's artery. Critchley [2] reported a case in which occlusion of Heubner's artery occurred with resultant weakness of the contralateral arm, mild weakness of face, palate and tongue, and aphasia. The lesion was in the left (major) hemisphere. According to Brock,[4] occlusion of the recurrent artery of Heubner causes paralysis of the contralateral shoulder, the lower part of the face and the tongue and an extrapyramidal type of rigidity or involuntary movement.

(*b*) Occlusion of the middle and posterior internal frontal branches. Critchley [2] reported a case in which these occlusions occurred, and the patient suffered contralateral hemiplegia, with eyes and head deviated to the opposite side.

(*c*) Occlusion of the paracentral artery. This results in weakness of the contralateral lower limb, or crural monoplegia. The weakness is greatest in the distal parts of the limb. Occasionally paresis of the contralateral arm and sides of face and tongue may occur.

In conclusion one can say that the outstanding symptoms from occlusion of the anterior cerebral artery include (1) paralysis of the contralateral lower extremity; (2) forced grasping and groping movements of the upper limb; (3) ideokinetic apraxia affecting the left arm, whether the occlusion be right or left sided; (4) mental changes—deterioration, emotional lability. Thrombosis of the vein of Rolando closely resembles occlusion of the paracentral artery.[2]

Bilateral lesions of the anterior cerebral artery cause weakness of the legs and almost no sensory change in reported cases. An aneurysm of the anterior cerebral artery near its origin may cause unilateral anosmia, progressive dimness of vision and primary optic atrophy. Aneurysms on the anterior communicating artery may cause bitemporal hemianopsia.

Dandy [8] expressed the belief that the center of consciousness lay in the left cerebral hemisphere along the mesial aspect of the hemisphere near the anterior part of the corpus callosum. According to him, if the left anterior cerebral artery was injured, the patient could never regain consciousness. Poppen [9] reported a series of 10 cases in which ligation of the left anterior cerebral artery was done, with success in 8 cases. Bilateral ligation was done successfully in 2 of these. He felt that if the blood pressure were kept within normal limits during the surgical procedure, ligation could be done without untoward changes in the state of consciousness and the collateral circulation would be adequate if anemia were not produced.

THE MIDDLE CEREBRAL ARTERY

Course.—The middle cerebral or sylvian artery, the largest terminal branch of the internal carotid artery, courses from its origin across the anterior perforated substance to enter the depth of the fissure of Sylvius and then curves outward to the external surface of the hemisphere. Before reaching the surface it gives off its main collateral branches, which come individually to the surface along the fissure.

Field of Distribution.—1. Basal branches:

(*a*) The superior half of the anterior and posterior divisions of the internal capsule.

(b) The superior half of the head of the caudate nucleus, and the horizontal part of the caudate nucleus.

(*c*) The external and middle segments of the nucleus lenticularis.

(*d*) The lateral parts of the anterior commissure.

2. Cortical branches:

(*a*) The superior, middle and inferior temporal gyri.

(*b*) The angular gyrus.

(*c*) The supramarginal gyrus.

(*d*) The superior parietal gyrus.

8. Dandy, W. E., The Brain, in Lewis, D.: The Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, p. 51.

9. Poppen, J. L.: Arch. Neurol. & Psychiat. **41**:495, 1939.

(*e*) The inferior three fourths of the precentral and postcentral gyri.

(*f*) The internal orbital gyrus.

Branches.—1. Perforating branches: These are given off at right angles from the trunk at the anterior perforated space. They penetrate perpendicularly through it. They are small and numerous. Foix and Levy [10] distinguished three groups:

(*a*) The putaminocapsular, supplying the putamen, the internal capsule and the caudate nucleus.

(*b*) A few external pallidal branches to the lateral part of the globus pallidus.

(*c*) Inconstant pallido-optic branches to the globus pallidus and the thalamus.

2. Cortical branches:

(*a*) The anterior temporal artery gives branches to the rostral third of the temporal gyri and the insula.

(*b*) The orbital sulcal branches supply the lateral part of the orbital surface of the frontal lobes and the external surface of the inferior frontal convolution except for the opercular area.

(*c*) The artery of the prerolandic fissure supplies the foot and anterior lip of the precentral gyrus, the foot of the middle frontal convolution and the opercular part of the inferior frontal convolution.

(*d*) The artery of the rolandic fissure supplies the posterior border of the precentral gyrus and the most anterior border of the postcentral gyrus.

(*e*) The anterior parietal artery supplies the posterior border of the postcentral gyrus and the anterior portion of the other parietal convolutions.

(*f*) The posterior parietal artery supplies the supramarginal gyrus and posterior part of the parietal lobe.

(*g*) The artery of the angular gyrus is a continuation of the middle cerebral artery and supplies the angular gyrus.

(*h*) The posterior temporal artery irrigates the posterior two thirds of the superior temporal and the posterior half of the middle temporal convolutions.

It is important to note that the branches of the middle cerebral artery are predominantly arteries of fissures and irrigate the margins of the two adjacent convolutions.

10. Foix, C., and Levy, M.: Rev. neurol. **34** (pt. 2):1, 1927.

Syndromes of the Middle Cerebral Artery.—1. Complete occlusion of the middle cerebral artery causes contralateral hemiplegia, hemianesthesia and hemianopsia, and global aphasia if the lesion involves the major hemisphere. It is usually fatal.

2. Occlusion of the deep branches of the middle cerebral artery results in destruction of most of the putamen, all of the superior part of the internal capsule and the outer segment of the globus pallidus. The clinical findings vary from a moderate degree of hemiplegia of equal severity in both extremities to severe hemiplegia, usually with more marked involvement of the lower extremity. Hemianopsia or sensory defect does not usually arise. Aphasia can result if the lesion is on the major side. Partial involvement of the perforating arteries constantly produces hemiplegia due to involvement of the internal capsule. Hemichorea also occurs at times, possibly due to involvement of the corpus striatum.

3. Occlusion of the prerolandic artery causes contralateral weakness of the lower part of the face and of the tongue. It occasionally produces slight weakness of the hand (Grinker [11]). If the major hemisphere is involved, there will be motor aphasia.

4. Occlusion of the rolandic artery causes contralateral hemiplegia of a variable degree.

5. Occlusion of the anterior parietal artery causes contralateral defects in gnostic sensation with slight weakness of the upper extremity. Lesions of the major parietal lobe may also cause amnesic aphasia.[7]

6. Occlusion of the posterior parietal and angular artery causes hemianopsia and mild sensory defects. If on the major side, it also causes aphasia of the type described under lesions of the angular artery. Involvement of the posterior parietal artery causes damage of the supramarginal gyrus with consequent ideomotor apraxia.[7]

7. Occlusion of the angular artery on the major side causes visual verbal agnosia with agraphia. Gerstmann's syndrome (acalculia, confusion of laterality, "finger agnosia" and agraphia) occurs with lesions at the border of the major angular gyrus on the occipital lobe.[7]

8. Occlusion of both the posterior temporal and the angular arteries causes hemianopsia plus aphasia of one or a combination of the types named under the individual arteries.

9. Occlusion of the posterior temporal artery causes hemianopsia, due to softening of the visual radiation, and aphasia if the lesion is in the major hemisphere. If Wernicke's area is affected, there is acoustic

11. Grinker, R. R.: Neurology, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1937.

verbal aphasia.[7] Wernicke's aphasia occurs if the superior temporal convolution is involved.[7]

THE ANTERIOR CHOROIDAL ARTERY

Course.—The anterior choroidal artery arises from the internal carotid artery between the origins of the posterior communicating and middle cerebral arteries. It then crosses the optic tract and runs posteriorly along the medial border of the tract against the cerebral peduncle. At the lateral geniculate body it divides into many branches, most of which recross the optic tract to enter the inferior horn of the lateral ventricle and reach the choroid plexus. The two terminal branches run posteriorly over the lateral geniculate body to join the posterior cerebral and posterior choroidal ateries.

Field of Distribution.—1. The optic tract.

2. The anterior third of the pes pedunculi.

3. The posterior two thirds to four fifths of the inferior half of the posterior limb of the internal capsule.

4. The optic radiation.

5. The tail of the caudate nucleus.

6. The inner segment of the lenticular nucleus.

7. The choroid plexus in the descending and posterior cornua.

8. The amygdaloid nucleus.

9. The outer part of the anterior commissure.

10. The uncinate gyrus.

Abbie [3] included the substantia nigra, the nucleus ruber, the subthalamic body, the ventral lateral nucleus of the thalamus, the lateral and anterior parts of the lateral geniculate body, the stria terminalis and most of the globus pallidus.

Branches [12].—1. Nearest the origin of the vessel, branches arise to supply the tail of the caudate nucleus and the outer border of the anterior commissure.

2. Some vessels reach the uncus gyri hippocampi and supply the posteromedial part of the underlying amygdaloid nucleus. These anastomose with branches of the middle and posterior cerebral arteries.

3. A number of vessels go to the anterior inferior part of the hippocampus and the dentate gyrus. These anastomose with branches of the posterior cerebral artery.

4. More posteriorly a series of branches penetrate the optic tract and then pass dorsally into the base of the brain to reach:

(*a*) The inferior half of the posterior limb of the internal capsule.

12. Steegmann, A. T., and Roberts, D. J.: J. A. M. A. **104**:1695, 1935.

(*b*) The internal segment of the lenticular nucleus.

(*c*) The beginning of the optic and acoustic radiation.

5. Branches reach the cerebral peduncle, where they anastomose with branches from the posterior communicating and posterior cerebral arteries. They supply the middle third of the crus cerebri, the upper part of the substantia nigra and nucleus ruber, the subthalamic body and often the most superficial part of the ventral lateral nucleus of the thalamus.

6. From the main trunk or from one of the terminal divisions arises a constant vessel which enters the stria terminalis and the tail of the caudate nucleus. It then runs posteriorly and dorsally in these to the level of the junction of the body and the temporal horn of the lateral ventricle.

7. Branches to the lateral and anterior aspects of the lateral geniculate body. The medial and posterior aspects of the lateral geniculate body are supplied by the posterior cerebral artery. The macular area in the lateral geniculate body is supplied by both of these vessels.[12]

Clinical Significance.—The symptoms resulting from occlusion of the anterior choroidal artery are as follows:

1. Hemiplegia in all cases. In a case reported by Kolisko [14] there was no involvement of the anterior half of the posterior limb of the internal capsule and the hemiplegia probably was on the basis of involvement of the crus.

2. Hemianesthesia. This occurs constantly but is usually incomplete. It involves all forms of sensation.

3. Hemianopsia. This is recorded by Schiff-Wertheimer [15] and Ley [16] but not by Kolisko. In a case of Mackenzie's (reported by Abbie [3]) in which both anterior choroidal arteries were involved, the hemianopsia was a bilateral homonymous superior quadrantic defect with macular fields spared, indicating involvement of the lateral parts of the lateral geniculate bodies.

At autopsy in patients with occlusion of the anterior choroidal artery there is found degeneration in the posterior limb of the internal capsule, the greater part of the globus pallidus and the cerebral peduncle. Degeneration has also been observed in the lateral aspect of the lateral geniculate.[3] A few authors have reported involvement also of the head

13. Abbie, A. A.: Anat. **67**:491, 1933.

14. Kolisko, A.: Ueber die Beziehung der Arteria choroidea anterior zum hinteren Schenkel der inneren Kapsel des Gehirnes, Vienna, A. Hölder, 1891.

15. Schiff-Wertheimer, S.: Les syndromes hémianopsiques dans le ramollissement cérébral, Thesis, Paris, no. 584, 1926.

16. Ley, J.: J. de neurol. et de psychiat. **32**:785 and 895, 1932.

of the caudate nucleus, the anterior commissure and the amygdaloid nucleus.

THE POSTERIOR COMMUNICATING ARTERY

Course and Distribution.—The posterior communicating artery arises from the internal carotid artery just before it divides into the anterior and the middle cerebral artery. It passes posteriorly to join the posterior cerebral artery. It sends branches to the following structures:

1. The optic chiasm and the tuber cinereum.
2. The subthalamic region.
3. The pes pedunculi—anterior third.
4. The anterior fifth or third of the posterior division of the internal capsule.
5. The external and internal nuclei of the thalamus.

Clinical Significance.—The clinical conditions resulting from occlusion of the posterior communicating artery are variable and indefinite. Brock [4] reported contralateral mimetic facial paralysis.

THE POSTERIOR CEREBRAL ARTERY

Course.—The posterior cerebral arteries arise from the bifurcation of the basilar artery. Each runs outward and posteriorly around the cerebral peduncle. After receiving the posterior communicating branch from the internal carotid artery, it passes on to the inferior surface of the occipital lobe and divides into terminal branches.

Field of Distribution.—1. Basal branches:

- (*a*) Mamillary bodies.
- (*b*) The posterior two thirds of the pes pedunculi.
- (*c*) The nucleus ruber.
- (*d*) The thalamus. (The posterior half, the anterior nucleus, the anterior superior part of the external nucleus, the posterior half of the external nucleus, and the posterior third of the internal nucleus.)
- (*e*) The choroid plexus in the lateral ventricles.
- (*f*) The medial geniculate body and the medial and posterior aspects of the lateral geniculate body.
- (*g*) The body and posterior parts of the fornices.
- (*h*) The inferior part of the descending columns of the fornices.
- (*i*) Alpers [5] includes the posterior limb of the internal capsule in the field of supply of the posterior cerebral artery.

2. Cortical branches:

- (*a*) The inferior half of the inferior temporal gyrus.

(*b*) The medial surface of the fusiform gyrus, the lingual gyrus, the cuneus, and the quadrate gyrus.

Branches of the Posterior Cerebral Arteries.—1. The anterior temporal branch is directed forward over the inferior surface of the temporal lobe, where it supplies the anterior part of the fusiform and the hippocampal gyrus.

2. The posterior temporal branch is distributed to the rest of the inferior surface of the temporal lobe.

3. The large posterior occipital branch runs buried in the calcarine fissure and supplies the posteromedial and inferior portions of the occipital lobe, especially the lingual lobule and the cuneus.

4. A series of collaterals to the mesencephalon and the basal ganglions. These also supply almost all of the thalamic and peduncular regions, including the lateral half of the cerebral peduncle, the subthalamic region, the red nucleus, the corpus luysi, and the substantia nigra, the posterior inferior half of the thalamus, the superior cerebellar peduncles, the retrolenticular capsule, and the geniculate bodies.

Clinical Significance.—The posterior cerebral artery is rarely obliterated at its origin. Symptoms from such an occlusion are rare, since anastomoses via the posterior communicating artery may at times be very large, and peripheral branches of the posterior cerebral artery anastomose freely with neighboring arteries. If occlusion occurs, the patient usually gets crossed hemianopsia; if it is sudden, Brock [4] reported, temporary bilateral blindness may occur. If the posterior cerebral artery of the major side is occluded, the patient may also show the Charcot-Wilbrand syndrome (visual agnosia and loss of ability to revisualize images [7]). Crossed sensory and motor defects may occur from involvement of the thalamus, the posterior limb of the internal capsule and the cerebral peduncle. According to Foix and Masson,[17] complete occlusion of the posterior cerebral artery on the major side will cause: (1) hemianopsia, (2) pure alexia and (3) sensory-motor disturbances—hemiparesis and a thalamic syndrome.

If the lesion is in the other hemisphere, thalamic pain is predominant and alexia is absent.

Partial involvement of the posterior cerebral artery causes alexia, hemianopsia and cortical blindness. Foix termed these partial syndromes "partial anterior pedunculo-thalamo-subthalamic syndromes." He divided them into the following types:

1. Cerebellar peduncular type. This type most commonly shows a homolateral cerebellopyramidal syndrome or a predominantly cerebellar

17. Foix, C., and Masson, A.: Presse méd. **31**:361, 1923.

syndrome associated with involvement of the medial longitudinal fasciculus.

2. The thalamic syndrome—monoplegic form. This type shows thalamic symptoms, with or without monoplegia, and cerebellar symptoms. It is due to occlusion of the branches going to the thalamus and consists of hemiparesis, occasionally complete hemianesthesia, hemichorea and central pain. Hemianopsia may also occur.

Summary of the Findings Most Common in Patients with Occlusions of the Cerebral Vessels

Vessel	Contralateral Motor Signs	Contralateral Sensory Signs	Aphasia*	Visual Field Defects	Mental Changes	Apraxia
Internal carotid artery	Hemiplegia	Hemianesthesia	Complete	Homonymous hemianopsia; ipsilateral blindness or primary optic atrophy (ophthalmic artery)	.....	.....
Anterior cerebral artery	Hemiplegia, particularly of proximal part of arm and distal part of leg (leg most affected)	Hypesthesia of leg	Mild, transient motor	.....	Intellectual loss, emotional instability	Left ideokinetic apraxia
Heubner's artery	Hemiplegia (mild VII and XII, and proximal part of arm); extrapyramidal rigidity and involuntary movements	.....	Mild motor	.....	.....	.....
Paracentral artery	Distal part of leg; occasionally arm, VII and XII	.....	.....	.....	.....	.....
Middle cerebral artery	Severe hemiplegia (arm most severe), dysarthria	Hemianesthesia	Global	Hemianopsia; if partial, of lower quadrant type	.....	Ideokinetic apraxia
Anterior choroidal artery	Hemiplegia (arm and leg equally affected)	Hemianesthesia, usually incomplete; partial thalamic sensory change, especially in arm	.....	Hemianopsia or upper quadrant defect	.....	.....
Posterior cerebral artery	Hemiparesis, hemiataxia, choreoathetosis; occasionally Weber's syndrome	Hemianesthesia, thalamic pain	Aphasia-alexia most common	Hemianopsia, complete or partial; lower quadrant defect	.....	.....

* Aphasia is present only if the lesion is on the major side.

3. The syndrome of the suboptic region. There are two types of suboptic involvement. The first shows Weber's syndrome with pyramidal hemiplegia replaced by cerebellar hemiplegia. The lesion is in the inferior part of the red nucleus and involves the medial longitudinal fasciculus. The second shows a thalamocerebellar syndrome with occasional hemianopsia. It is due to a lesion of the red nucleus extending up into the thalamus.

Alpers [5] included a syndrome of hemiplegia, hemianesthesia and hemianopsia (similar to that described as due to occlusion of the anterior choroidal artery) and attributed it to the branch of the posterior cerebral artery which supplies the posterior limb of the internal capsule. Nielson [7]

contended that a lesion of the major occipital lobe causes visual autotopagnosia and optical disorientation in space.

Numerous similarities of the various syndromes may be noted in the foregoing summary. However, definite differential points exist and should suffice so that localization may be made with relative ease if adequate study of the patient is made. It is noteworthy that a small lesion produced by occlusion of the anterior choroidal artery may produce clinical symptoms so similar to those of an extensive lesion due to a closure of the middle cerebral artery. Speculation about the size of the lesion as judged by the patient's general state (changes in sensorium) may also aid in differentiation.

The overlap in the fields of distribution of the cerebral vessels is fortunate for the patient but confusing for the diagnostician. For example, the internal capsule receives supplies from four vessels (Beevor [1]). The inferior half of its anterior limb is supplied by the anterior cerebral artery; the superior half, by the middle cerebral artery. The anterior part of the genu is supplied by the anterior cerebral artery; the posterior half, by the posterior communicating artery. The superior half of the posterior limb is supplied by the middle cerebral artery, the inferior half is supplied by the posterior communicating artery (in the anterior one third) and the anterior choroidal artery (in the posterior two thirds).

SUMMARY

A review of the syndromes of the cerebral vessels is presented in an effort to clarify and organize the available material and thus to enhance the practical application.

News and Notes

Appointment.—Russell S. Fisher, resident fellow in legal medicine in Harvard Medical School, Boston, has been appointed assistant professor of pathology in the Western Reserve University School of Medicine, Cleveland.

Congress on Cancer.—The Fifth International Congress for Scientific Research and the Social Fight Against Cancer is to be held at the Sorbonne in Paris, France, July 17 to 22, 1950. A. Lacasagne is president of the congress. Correspondence can be directed to Prof. V. LeLorier, Secretary-General of the Congress, 6 Avenue Marceau, Paris 8, France.

Research on the Betatron.—The United States Public Health Service has awarded $15,000 to the University of Illinois College of Medicine in support of research studies involving the 22,000,000 volt betatron. The grant will be used specifically for the study of the effects of the betatron x-ray beam on bone and cartilage, under the supervision of Roger A. Harvey, of the department of radiology, and Granville A. Bennett, of the department of pathology.

Medicolegal Laboratory.—A medicolegal laboratory, operated under a cooperative arrangement of Houston County, the University of Texas and the M. D. Anderson Foundation, was established recently in Houston, Texas, in the Jefferson Davis Hospital. The laboratory is headed by W. W. Coulter Sr., chief pathologist at the hospital, with Charles A. Dwyer Jr., county physician, as assistant. The laboratory, which will be used in teaching medicolegal pathology in the University of Texas Postgraduate School of Medicine, is under the general direction of William O. Russell, head of the department of pathology of the University of Texas Medical Branch, Galveston.

The American Society of Clinical Pathologists will hold its twenty-eighth annual meeting in Chicago at the Drake Hotel on October 12, 13, 14 and 15.

The Academy of Forensic Sciences (American Medico-Legal Congress) will hold its second meeting in Lincoln Hall, Northwestern University School of Law, Chicago, on Jan. 26, 27 and 28, 1950. The meeting will be devoted to a discussion of problems of forensic science and a formal organizational program. Address A. W. Freireich, 180 Hempstead Avenue, Malverne, N. Y., or Ralph F. Turner, Acting Secretary, Department of Police Administration, Michigan State College, East Lansing, Mich.

Books Received

HISTOPATHOLOGY OF IRRADIATION FROM EXTERNAL AND INTERNAL SOURCES. Edited by William Bloom, M.D., professor of anatomy, Department of Anatomy and Institute of Radiobiology and Biophysics, University of Chicago. National Nuclear Energy Series, Manhattan Project Technical Section. Pp. 808, illustrated. Price, $8. New York, Toronto, London: McGraw-Hill Book Company, 1948.

This is the first volume to be published of approximately sixty monographs entitled the National Nuclear Energy Series, which will record the research done and the technical methods developed during the war by various groups working under the Manhattan Project or, more recently, the Atomic Energy Commission. This volume is one of a series of monographs called the Plutonium Project Record and is a report of a part of the health work carried on mostly by the Metallurgical Laboratory at Chicago during the three year period from 1942 to 1945.

Each chapter is written by an individual author and is the description of the histologic changes observed in a single organ or an organ system following external or internal application of radiation. This organization allows for ready comparing of lesions in a single organ under different kinds and doses of radiation but makes comparing of different organs under such circumstances difficult. Since this work was done under a single director, the criteria of damage were uniform and quite accurate comparisons can be made among the biologic effects of different types of radiation, i. e., roentgen, slow neutron, fast neutron, and alpha, beta and gamma radiation. The abundant amount of data on histologic changes resulting from internal irradiation should be of considerable value to those interested in using radioactive isotopes. The absence of data concerning the metabolism of the radioactive elements makes it impossible to determine the amount of internal radiation delivered to an organ; however, as such information becomes available in the literature the value of this work should be greatly enhanced. Dr. Bloom modestly states in the introduction that there is little in this book that can be considered new. However, the descriptions of bone lesions following the administration of bone-seeking radioactive isotopes and the emphasis on the radiosensitivity of the erythroblast seem to the reviewer to be important contributions. Also, some controversial points seem to have been settled, e. g., the radiosensitivity of the spermatogonia.

The book, by and large, reports objective findings, and there is little speculation concerning the mechanism of the biologic effects of ionizing radiation. For this reason the casual reader may find it tedious; the introduction and the summaries of each chapter, however, are good and should be interesting and informative to such a reader. The worker interested in specific problems will find it of considerable aid as a reference. The book is printed on slick paper and is copiously illustrated with photomicrographs and a few camera lucida colored drawings. Some of the photomicrographs are not very clear; others are quite good. Errors are gratifyingly few. The bibliography is large and well selected.

When one considers that after the war many of the scientists working for the Manhattan Project were anxious to return to their peacetime pursuits and that the recording of the wartime work necessarily was done quickly and under pressure if it was to be done at all, most of the criticisms that might be leveled at the book are dispelled.

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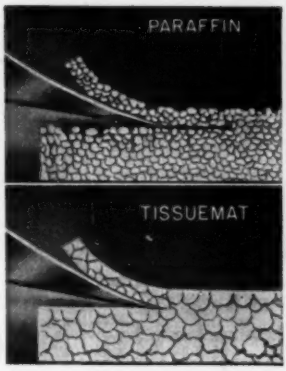

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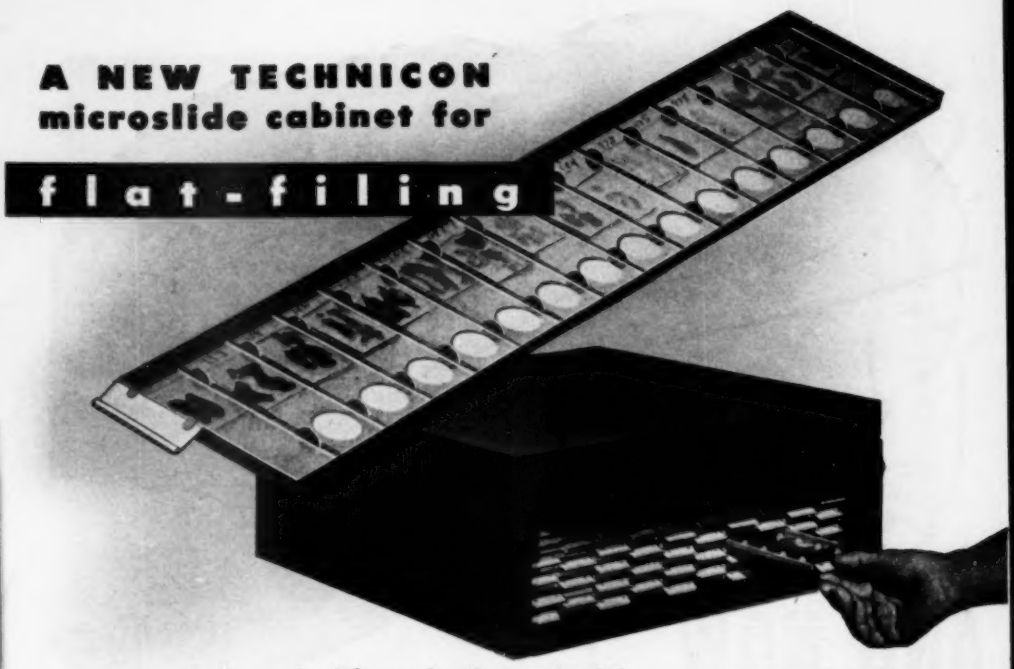

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